Diabetes care in old age

Hans van Hateren

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Stellingen behorende bij het proefschrift

DIABETES CARE IN OLD AGE

1. Ouder worden is de belangrijkste risicofactor voor sterfte, de andere risicofactoren worden met het ouder worden steeds minder belangrijk *(dit proefschrift)*.

2. Oversterfte door behandeling met bloeddrukverlagende medicatie valt niet uit te sluiten, zeker niet bij de kwetsbare oudere *(dit proefschrift)*.

3. Het uitvragen van orthostase klachten is belangrijker dan het meten van orthostase *(dit proefschrift)*.

4. Zorgverleners moeten actiever worden in het passief zijn *(dit proefschrift)*.

5. In grote gerandomiseerde studies worden vaak die patiënten geïncludeerd die het meeste baat bij een behandeling hebben *(o.a. dit proefschrift)*.

6. Studies bij ouderen zouden altijd de mate van kwetsbaarheid van de patiënten moeten vastleggen.

7. De huidige richtlijngeneeskunde is een potentieel gevaar voor het leveren van goede zorg aan ouderen.

8. Belangenverstrengeling leidt tot slechte richtlijnen.

9. "It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines." *(Marcia Angell, former editor-in-chief of the New England Journal of Medicine)*.

10. De spilfunctie van de huisarts in de gezondheidszorg is essentieel voor continuïteit van zorg.

11. Beter 'oud en vertrouwd' dan 'nieuw en onbekend' *(Jan Palmen, kaderhuisarts diabetes)*.

12. Marktwerking in de gezondheidszorg is een geloof.

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Content

Chapter 1

Introduction

The worldwide prevalence of diabetes is high and still increasing [1-3]. The number of people with diabetes in 2010 was estimated to be 285 million worldwide [3]. Two decades ago, it was expected that the number of people with diabetes in the Netherlands would increase from 200.000 in 1990 to 350.000 in 2005 [4]. The actual number of patients with diabetes in 2005 appeared to be twice as high, and in 2007 the diabetes prevalence was estimated to be 740.000. For 2025, it is projected that the number of people with diabetes will even rise to 1.3 million [4]. Some later estimates even point towards a prevalence of 950.000 subjects in the Netherlands with diabetes in 2010, thus necessitating a readjustment of the projection for 2025 to 1.6 million (estimate based on combination of SFK information and results from the ZODIAC database). Although obesity and lifestyle are the most important contributors, increased life-expectancy for patients with diabetes, growth of the population worldwide and ageing of the Western population all contribute to the current diabetes epidemic. In the Netherlands, the proportion of patients aged older than 65 years is expected to increase from 14% in 2005 to 21% in 2025 [4]. In the 'Zwolle Outpatient Diabetes project Integrating Available Care' (ZODIAC) study, a shared care project for patients with type 2 diabetes mellitus (T2DM), more than one quarter of the participating patients is older than 75 years.

Absence of evidence in old age

Cardiovascular risk management is inextricably bound up with the care for patients with T2DM in an effort to prevent or alleviate macrovascular complications [5,6]. Interventions aimed at optimizing cardiovascular risk protection, such as antihypertensive and cholesterol lowering treatment, have proven to be effective in reducing cardiovascular complications in patients with T2DM [7-9]. However, as evidently clear as the published data may seem to be regarding the efficacy of the different (drug) interventions to prevent cardiovascular morbidity and mortality, very little is known about the effectiveness of many of these interventions in subjects with T2DM older than 75 years.

There are several issues with respect to cardiovascular risk management in old age that need some consideration. Firstly, there are no randomised controlled trials whatsoever that have specifically investigated the effects of any cardiovascular risk modifying intervention in this specific population. Secondly, there is an underrepresentation of elderly patients in clinical trials of cardiovascular disease in the general population [10,11]. This underrepresentation does also exist for subjects with T2DM. Arbitrary upper age limits are used in almost all trials, being mostly 75-80 years. An overview of the age limits used in large randomised controlled trials is presented in table 1 [12-33]. The mean age of the participants is well below 70 in most trials. Although the absolute number of type 2 diabetic patients >75 years in some trials is probably large enough to allow separate analyses, unfortunately, these analyses have not been

performed, except for the ADVANCE trial [34]. Participation of elderly patients is also limited because of the presence of exclusion criteria, besides age itself, which strongly correlate with advancing age, including common medical conditions and commonly prescribed drugs [11]. These exclusion criteria and arbitrary age limits result in selection bias and, as a consequence, in difficulties translating the results of these trials to the T2DM population older than 75 years.

Study (references)	Number of T2DM patients (total population)	Age limits	Age (SD)
Multi-intervention trials			
ALLHAT (12)	12.063 (33.357)	≥ 55	66 (6)
ADVANCE (13)	11.140 (11.140)	≥ 55	66 (6)
ASCOT (14)	5.137 (19.342)	40-79	63 (8)
UKPDS (15)	4.054 (4.054)	25-65	56 (8)
ACCORD (16)	10.251 (10.251)	≥ 40	62 (9)
ADDITION (17)	3.055 (3.055)	40-69	60 (7)
Glucose-lowering trials			
VADT (18)	1.791 (1.791)	-	60 (9)
RECORD (19)	4.447 (4.447)	40-75	58 (8)
PRO-ACTIVE (20)	5.238 (5.238)	35-75	62 (8)
Lipid-lowering trials			
HPS (21)	5.963 (20.536)	40-80	62 (9)
CARDS (22)	2.828 (2.828)	40-75	62 (8)
MEGA (23)	1.632 (7.832)	40-70	58 (7)
LIPID (24)	589 (9.014)	31-75	62 (55-67)
TNT (25)	1.501 (10.001)	35-75	63 (8)
IDEAL (26)	1.069 (8.888)	≤ 80	62 (10)
PROSPER (27)	623 (5.804)	70-82	75 (3)
Hypertension trials			
PROGRESS (28)	762 (6.105)	30-90	64 (8)
STOP Hypertens-2 (29)	719 (6.614)	70-84	76 (?)
Syst-EUR (30)	492 (4.695)	≥ 60	70 (7)
SHEP (31)	583 (4736)	≥ 60	70 (6)
HOT (32)	1.501 (18.790)	50-80	62 (8)
HYVET (33)	263 (3.845)	≥ 80	84 (3)

Table 1. Age limits and number of included patients within large trials in patients with cardiovascular disease and/or type 2 diabetes mellitus. Age is represented as mean (standard deviation (SD)) or as median (interquartile range (IQ)).

Thirdly, there is no clear definition of 'old age'. A recent expert consensus document on hypertension treatment in old age also acknowledged that the definition of elderly patients is vague and not well-defined [35]. Many RCTs and meta-analyses that aimed to study interventions in 'old age' used 65 years as a cut-off value [36,37]. However, more than one quarter of the type 2 diabetic population in primary care in the Netherlands is older than 75

years! Using a cut-off value of 65 years in the ZODIAC cohort would mean that approximately 60% of the population should be considered as being old.

It can be concluded that the evidence for effective cardiovascular risk management in elderly diabetic patients, defined as those aged older than 75 years, is to a large extent absent. Therefore, the application of current diabetes guidelines to this specific population should be questioned [38,39]. Although several guidelines for diabetes care in old age have been published in the past decades, their recommendations are mainly based on expert opinion or trials and meta-analyses performed in patients aged older than 65 years [39-42]. Generally speaking, translating the results of trials into recommendations for daily practice should only be done when the patients included in these trials resemble the patients in daily practice. In other words, it should be questioned whether there are enough similarities between elderly diabetic patients and their younger counterparts that justify using the results of trials in younger patients for developing guidelines for elderly patients.

Elderly patients with T2DM: a population on its own?

By all means, the elderly population is a selected one, in the sense that these patients have shown to be able to survive to the age they have reached. In 2010, the chance of reaching the age of 85 years for a male newborn was 15%, whereas this chance was almost 30% for a man of 80 years (http://statline.cbs.nl/StatWeb/). These numbers illustrate that age itself is an important determinant of a individuals life expectancy, and also that life expectancy of elderly patients should not be underestimated. On the other hand, life expectancy in absolute terms does decrease with advancing age and as a result there is also less time left to develop new diabetes-related complications, which often take many years to develop. This is of special interest for patients with diabetes diagnosed at a higher age. Elderly patients with diabetes of short duration have much lower rates of microvascular complications compared to those with long-standing diabetes [43,44]. Furthermore, elderly patients, especially those with diabetes of short duration, seem to be at lower risk for serious complications like proliferative and vision-threatening retinopathy [45,46].

In contrast to microvascular complications, the differences between diabetes of short and long duration are much smaller with respect to the prevalence of macrovascular complications [43]. Whereas diabetes duration seems to be the most important factor in developing retinopathy, the risk for macrovascular complications and mortality is modified by many other variables, of which age itself is the most important risk factor. The absolute effect of T2DM on the risk of cardiovascular events and mortality declines with advancing age through the phenomenon of competing risks: elderly patients have many other risk factors, so the additional effect of T2DM is relatively small [47].

Another important characteristic of elderly patients is that they exhibit large differences in health status, ranging from very healthy to very frail [40,41]. In general, elderly patients with diabetes have higher rates of functional impairment and disability, caused by the higher prevalence of complications and comorbidities [48,49]. Firstly, cardiovascular and diabetes-related complications are more prevalent in elderly diabetic patients [43,50]. Also, various age-related comorbidities, such as urine incontinence, cognitive decline and depression, are also more prevalent in elderly patients with T2DM than those without [51-53]. These complications and comorbidities may in turn lead to a decreased quality of life.

The higher level of vulnerability with advancing age is also reflected in the caution that is warranted with certain drugs, because of e.g. decline in renal function. Take for example sulfonylurea derivatives; the risk for a hypoglycaemic event associated with these drugs is higher for the elderly compared to younger adults [54]. Another example is the use of antihypertensive drugs that may enhance the risk for orthostatic hypotension [55]. Preventing and recognizing orthostatic hypotension is important because of its association with falling, which may in turn result in fractures [56].

The facts presented in the previous paragraphs show that there can be no doubt that elderly patients should be considered as a population on their own. Based on the absence of evidence and the specific characteristics of the elderly population, the question arises whether the goal of diabetes management should be the same for elderly patients as it is for younger patients. It can be argued that the focus in old age should be more directed towards improving or maintaining quality of life instead of reducing complications and their associated mortality [57].

General aim and outline thesis

The general **aim of this thesis** was to study several aspects of diabetes care, specifically in old age, in order to provide evidence that can aid in clinical decision-making in daily practice and in tailoring important aspects of the guidelines forT2DM to this specific population.

In **Chapters 2-4** we focussed on the relationships between three important cardiovascular risk factors and mortality in old age. In these chapters, we investigated the relationships of glycemic control, lipids and blood pressure with all-cause and cardiovascular mortality. The main reason for performing these studies was the lack of randomised controlled trials showing beneficial effects of glucose-lowering, lipid-lowering and antihypertensive treatment in old age. Although some guidelines recommend applying less stringent HbA1c targets to frail older adults and those with limited life expectancy, the level of evidence of this advice is low

and mainly based on expert opinion [39-42]. The recommendations for lipid-lowering and antihypertensive treatment are mainly based on two randomised controlled trials in elderly patients from the general population [27,33]. Since these two studies included relatively healthy patients, and the number of patients with diabetes were small, no definite conclusions could be drawn for the ('average') elderly population with T2DM. For both lipids and blood pressure, observational studies in the general elderly population have even observed increased mortality with lower cholesterol levels and lower blood pressure [58-69]. In a cohort study from Finland, an inverse relationship between blood pressure and mortality was also observed in elderly patients with diabetes [70].

The study as described in **Chapter 5** was undertaken to investigate the effects of heart failure on the relationship between blood pressure and mortality. We hypothesized that heart failure could be an important confounder in this relationship. The midregional pro-A-type natriuretic peptide (MR-proANP) was determined and used as a marker of heart failure.

In **Chapter 6** we investigated whether and in what way estimated glomerular filtration rate (eGFR) was associated with mortality in old age. Although a substantial part of the older population has an eGFR <60 ml/min/1.73m^2, the clinical significance of a lower eGFR in older people is unclear [71-73]. A decrease in eGFR is physiological with advancing age. However, it can also be argued that it in some part reflects the high prevalence of kidney disease at older age.

The relationship between health-related quality of life (HRQOL) and mortality was assessed in **Chapter 7**. Poor HRQOL is related to adverse outcomes in patients with T2DM, including poor response to therapy, disease progression and even mortality [74-78]. Since advancing age is associated with functional disability in T2DM, and these disabilities can have a detrimental effect on a patient's quality of life, we were interested to know whether HRQOL was also associated with mortality in elderly T2DM patients as it is in younger adults with diabetes [78]. These results can aid in the discussion about the balance in focus between 'improving or maintaining quality of life' and 'reducing complications and their associated mortality' in elderly T2DM patients.

The prevalence of orthostatic hypotension, and its relationship with various clinical variables, amongst others fall risk, was investigated in a cross-sectional observational study (**Chapter 8**). Orthostatic hypotension (OH) is increasingly recognised as an important risk factor for cardiovascular disease and mortality. Although OH is more prevalent in old age, and in patients with diabetes, its prevalence in elderly patients with T2DM is unknown [79,80]. The potential adverse effects of orthostatic hypotension, such as falling, could be devastating and underline the importance of recognizing OH in old age.

In a study from France, trends in quality of care in type 2 diabetic patients aged 65 and older were investigated. Although quality of care and control of cardiovascular risk factors improved, the authors concluded that further improvement was still required [81]. Data on quality of care in the population aged older than 75 years are limited. Therefore, we investigated in **Chapter 9** the trends in quality of care as delivered in the ZODIAC cohort in the period 1998-2008.

In advance of the discussion of this thesis, as presented in **Chapter 11**, we put blood pressure treatment in elderly type 2 diabetic patients in perspective in **Chapter 10**. A new blood pressure target value for this population is proposed and the phenomenon of selection bias is illustrated in this chapter. After the general discussion of this thesis (**Chapter 11**), recommendations for daily practice and suggestions for future research are presented.

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Chapter 2

Glycemic control and the risk of mortality in elderly type 2 diabetic patients (ZODIAC-20)

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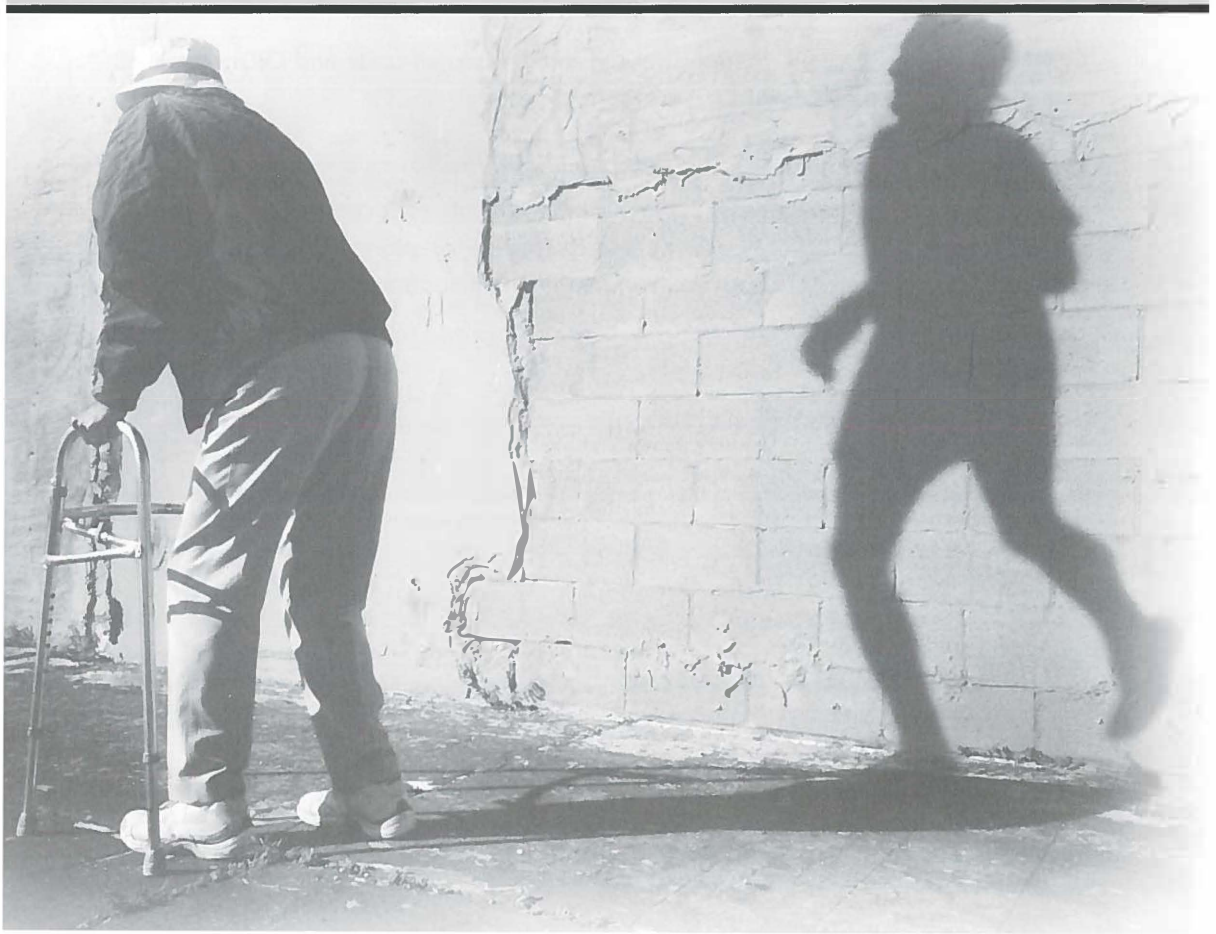

Abstract

Aims: Studies on macrovascular consequences of glucose control in elderly patients (>75 years) with type 2 diabetes mellitus (T2DM) are lacking. The present study aimed to investigate the relationship between HbA_{1c} and mortality in this specific population.

Methods: Between 1998 and 1999, 374 primary care patients with T2DM aged older than 75 years participated in the ZODIAC study, a prospective observational study. Early 2009, data on mortality were collected. Updated means for annually measured HbA_{1c} values were calculated after a follow-up time of 10 years. Updated mean HbA_{1c} was used as a time dependent covariate in a Cox proportional hazard model. Main outcome measures were all-cause and cardiovascular disease (CVD) mortality. Analyses were performed in strata according to diabetes duration (<5, 5-11 and ≥11 years).

Results: In the group with a diabetes duration <5 years, an increase of 1% in the updated mean HbA_{1c} level was associated with an increase in all-cause and CVD mortality risk of 51% (95%CI 17%-95%) and 72% (95%CI 19%-148%), respectively. Glycemic control was not related to mortality for patients with a diabetes duration ≥5 years.

Conclusions: Poor glycemic control is related to increased all-cause and CVD mortality in patients >75 years with T2DM of short duration (<5 years).

Discussion: Because of the observational study design, our results should be interpreted with caution. Nevertheless, they are suggestive that improving glycemic control may be beneficial in elderly patients with T2DM, especially in those with recently diagnosed T2DM. Randomised controlled trials are necessary to investigate whether this holds true.

Introduction

In a recent response to a meta-analysis of the Collaborators on Trials of Lowering Glucose (CONTROL) Group, the differences between patients with type 2 diabetes mellitus (T2DM) of short and long duration were emphasized [1,2]. Based on the heterogeneous results of four large randomised controlled trials, it seems that intensive glucose control is only beneficial in those with diabetes of short duration [3-6]. A meta-analysis, published in 2006, already showed that the beneficial effects of improved glycemic control decreased with longer diabetes duration and with increasing age [7]. Unfortunately, there are no clinical data on the macrovascular and microvascular consequences of (intensive) glucose control in adults older than 75 years. Although guidelines recommend to apply less stringent targets to frail older adults and those with limited life expectancy, the level of evidence of this advice is low and mainly based on expert opinion [8]. We aimed to explore the relationship between HbA_{1c} and (cardiovascular) mortality, and the role of diabetes duration in this relationship, in a prospectively designed cohort of elderly patients (>75 years) with T2DM.

Patients and methods

Study population

This study is part of the ZODIAC (Zwolle Outpatient Diabetes project Integrating Available Care) study; the design and details of which have been presented elsewhere [9]. In this study, general practitioners are assisted by hospital-based diabetes specialist nurses in their care of patients with T2DM. At baseline, patients with a very short life expectancy (including patients with active cancer) or insufficient cognitive abilities were excluded (~5%). Four patients were excluded because of insufficient baseline data. Nearly 90% (n=1357) of the remaining patients agreed to participate. For the present study, we selected all patients aged older than 75 years (n=374).

Data collection

Baseline data were collected in 1998 and 1999, and consisted of a full medical history including macrovascular complications, medication use, and tobacco consumption. Patients were considered to have macrovascular complications when they had a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke or transient ischaemic attack. Laboratory and physical assessment data, such as HbA_{1c}, lipid profile, serum creatinine, the urinary albumin-to-creatinine ratio, blood pressure, weight, and height were collected annually. An updated mean of annually measured HbA_{1c} was calculated for each individual from baseline to the end of the follow-up period by averaging the baseline values with the mean annual values. For example, at one year the

updated mean HbA_{1c} is the average of the baseline and one year values, and at three years it is the average of baseline, one year, two year and three year values. This technique is similar to the one used in the United Kingdom Prospective Diabetes Study (UKPDS) [10].

Clinical endpoints

We examined two clinical endpoints in this study: all-cause and cardiovascular disease (CVD) mortality. Early 2009, the vital status and cause of death were retrieved from records maintained by the hospital and the general practitioners. The causes of death were coded according to The International Classification of Diseases, 9th revision (ICD-9).

Statistical analyses

Continuous variables are presented as mean (± standard deviation) for normally distributed values and as median (interquartile range) for non-normally distributed values. Normality was evaluated using Q-Q plots. Nominal variables are presented as the total number of patients (percentage). A Cox proportional hazard model was used to investigate the relationship between the updated mean HbA_{1c}, as a time dependent covariate, and mortality with and without adjustment for selected confounders. We used two different models. In model 1, only age and gender were taken into account as possible confounders. In model 2, we adjusted for the following variables: age, gender, smoking (yes or no), BMI, duration of diabetes, serum creatinine, macrovascular complications (yes or no), albuminuria (yes or no), systolic blood pressure, total cholesterol-HDL ratio, and use of insulin (yes or no). Analyses were repeated in strata according to diabetes duration. The diabetes duration variable at baseline was categorised into tertiles: <5 (n=111), 5-11 (n=139) and ≥ 11 years (n=124). In order to estimate the possible implications of higher HbA_{1c} levels on mortality, we calculated the population attributable risk percent (PAR%) of HbA_{1c} levels ≥7% for all-cause and cardiovascular mortality [11]. In our analyses PAR% can be interpreted as the percentage by which mortality rates could be reduced if all patients would have had HbA_{1c} levels <7%. The assumption of proportional hazards was checked by inspecting the Schoenfeld residual plots for the baseline predictor variables. All analyses were performed with SPSS version 15.0.1 (SPSS inc., Chicago, Illinois, USA).

Ethics statement

The ZODIAC study and the informed consent procedure were approved by the local medical ethics committee. Informed consent was obtained from all patients.

Results

Baseline characteristics of our study population are presented in table 1. Approximately one third of our study population was male. Median age (interquartile range) was 80 (78-83) years and median diabetes duration was 8 (4-13) years. Patients with a diabetes duration ≥11 years (tertile 3) had lower mean BMI and were more often smokers compared to patients with shorter diabetes duration. The number of patients treated with only a diet was the highest in the group with a diabetes duration <5 years (tertile 1); also, use of insulin was the lowest in this group compared to patients with longer diabetes duration. After a follow-up time of 10 years, 304 out of 374 patients (81%) had died, of whom 127 deaths (42%) were attributable to cardiovascular causes.

	Overall	Diabetes duration			p-value
		Tertile 1 (<5 years)	Tertile 2 (5-11 years)	Tertile 3 (≥11 years)	
	n=374	*n=111*	*n=139*	*n=124*	
Age (years)	80 [78-83]	80 [78-83]	80 [77-82]	80 [78-84]	0.887
Male sex	130 (34.8)	34 (30.6)	57 (41.0)	39 (31.5)	0.148
Body mass index (kg/m²)	27.8 (4.4)	28.6 (4.4)	28.0 (4.3)	26.9 (4.2)	0.012
Duration of T2DM (years)	8 [4-13]	2 [1-3]	7 [6-9]	16 [13-20]	-
Systolic blood pressure (mm Hg)	155.7 (24.7)	153.1 (24.3)	156.8 (24.9)	156.7 (24.9)	0.416
Current smoking	33 (8.8)	4 (3.7)	11 (8.0)	18 (14.8)	0.011
HbA1c (%)	7.4 (1.2)	7.3 (1.3)	7.5 (1.1)	7.4 (1.2)	0.292
Albuminuria present	206 (55.1)	53 (47.7)	84 (60.4)	69 (55.6)	0.133
Cholesterol-HDL ratio	4.9 (1.6)	5.2 (1.7)	4.8 (1.6)	4.7 (1.5)	0.099
Serum creatinine (µmol/L)	98 [86-115]	95 [82-111]	99 [87-123]	98 [87-111]	0.165
Macrovascular complications present	162 (43.3)	45 (40.5)	62 (44.6)	55 (44.4)	0.780
Treatment T2DM					
- diet	40 (10.7)	19 (17.1)	13 (9.4)	8 (6.5)	0.025
- oral glucose lowering agents	265 (70.9)	85 (76.6)	102 (73.4)	78 (62.9)	0.050
- insulin	79 (21.1)	7 (6.3)	32 (23.0)	40 (32.3)	<0.001
Receiving antihypertensive treatment	231 (61.8)	71 (65.1)	82 (59.4)	78 (63.9)	0.610
Receiving lipid lowering treatment	17 (4.5)	5 (4.6)	8 (5.8)	4 (3.3)	0.627

Table 1. Baseline characteristics. Data are means (± SD), medians (interquartile range) or *n* (%). One-way ANOVA, Chi square, or Kruskal-Wallis test was used where appropriate to test for differences between groups.

Analyses overall group

In multivariate analyses (model 2), an increase of 1% in HbA_{1c} led to an increase in CVD mortality risk by 26% (95% confidence interval (CI) 6-49%). The unadjusted hazard ratio, and the age- and gender adjusted one, were not relevantly different. The relationship with all-cause mortality was not significant in both models.

Analyses stratified according to diabetes duration (table 2)

In the group with a diabetes duration <5 years (tertile 1), the level of HbA_{1c} as a continuous variable was positively related to both all-cause and CVD mortality. In multivariate analyses, an increase of 1% in HbA_{1c} was associated with an increase in all-cause and CVD mortality risk of 51% (95%CI 17%-95%) and 72% (95%CI 19%-148%), respectively. All results for patients with a diabetes duration ≥5 years were not significant.

Mortality	Model	Diabetes duration		
		Tertile 1 (<5 years) *n=111*	Tertile 2 (5-11 years) *n=139*	Tertile 3 (≥11 years) *n=124*
All-cause	Unadjusted	1.24 (1.01-1.52)	1.01 (0.83-1.24)	0.99 (0.82-1.20)
	Model 1 [a]	1.27 (1.03-1.55)	1.04 (0.85-1.26)	1.03 (0.84-1.26)
	Model 2 [b]	1.51 (1.17-1.95)	1.04 (0.84-1.28)	1.05 (0.85-1.30)
CVD	Unadjusted	1.35 (1.00-1.81)	1.17 (0.87-1.57)	1.19 (0.91-1.55)
	Model 1 [a]	1.37 (1.02-1.84)	1.19 (0.99-1.15)	1.28 (0.98-1.68)
	Model 2 [b]	1.72 (1.19-2.48)	1.18 (0.87-1.60)	1.16 (0.86-1.58)

Table 2. Analyses stratified according to diabetes duration. Hazard ratios and the 95% confidence intervals of HbA_{1c}, for all-cause and cardiovascular disease (CVD) mortality. [a] Adjusted for age and gender; [b] Adjusted for age, gender, smoking (yes or no), BMI, duration of diabetes, serum creatinine level, macrovascular complications (yes or no), albuminuria (yes or no), systolic blood pressure, total cholesterol-HDL ratio, and use of insulin (yes or no).

Population attributable risk percent

The PAR% of HbA_{1c} levels ≥7% for all-cause mortality in patients with diabetes of short duration was 23% (95%CI 2%-36%). For CVD mortality the PAR% was 39% (95%CI 17%-48%). Again, all results for patients with a diabetes duration ≥5 years were not significant.

All analyses were repeated with only the baseline HbA_{1c} value as variable of interest (data not shown). Results did not relevantly change. The proportional hazards assumptions were met for all analyses.

Discussion

Poor glycemic control is related to increased all-cause and CVD mortality in patients with T2DM aged over 75 years, but only in those with diabetes of short duration. In the lowest tertile (duration <5 years), the all-cause mortality risk was 51% higher for every 1% increase in HbA_{1c}. For CVD mortality, the increase in mortality risk was even 72%.

To our knowledge, the relationship between HbA_{1c} and mortality in elderly patients with T2DM has not been described before. In previous observational and intervention studies elderly patients were either not included or subanalyses were not performed for this specific population. More recently, a large retrospective observational study showed that there seems to be a U-shaped association between HbA_{1c} and mortality [12]. Although an estimated 16% of the study population was aged over 75 years, no subanalyses were performed.

It is important to emphasize that the associations found between HbA_{1c} and mortality in this study do not imply causality. Because of the observational nature of our study, we can only speculate about the underlying mechanisms. Firstly, poor glycemic control itself may indeed affect mortality risk in elderly patients with recently diagnosed diabetes. The heterogeneous results of four large randomised controlled trials in younger patients already suggested that intensive glucose control may only be beneficial with regard to mortality in those with diabetes of short duration [1,4-6,13]. Secondly, it may be possible that our results are influenced by confounders we did not adjust for. For example, the results for all-cause mortality may be confounded by co-morbidities such as cancer or infectious diseases. In order to reduce the impact of reverse causality we performed additional analyses for the overall group, in which we excluded the deaths in the first year of follow-up. This did not relevantly change the results.

Besides its observational design, there are other reasons why our results should be interpreted with caution. Firstly, our study cohort is rather small and only comprises 374 elderly patients with T2DM. Since we also stratified our cohort into tertiles, the number in these tertiles are even smaller. Secondly, the heterogeneous health status of elderly patients makes it more difficult to identify the implications of our results for clinical practice. However, additional analyses revealed that for patients with a diabetes duration less than 5 years, the all-cause mortality rate could theoretically have been lowered by 23% if all patients had had HbA1c levels <7%. An important strength of our study is its prospective design. Other strengths of our study are the high number of deaths after 10 years follow-up, the use of the updated mean method and the number of variables we adjusted for in our model.

Although our study is the first study linking higher levels of HbA_{1c} to increased mortality in elderly patients with recently diagnosed diabetes, we do not recommend aiming for intensive glycemic control for all subjects in this specific patient category. Intensive control may also lead to an increased risk of hypoglycemia causing possible adverse events such as fall accidents and fractures. Physicians caring for older patients should take co-morbidity, frailty and estimated life expectancy into account when setting treatment goals for individual patients. Confirmation of our results in other cohorts would be interesting, because if confirmed, randomised controlled trials are necessary to investigate whether improving glycemic control in specific elderly diabetic populations, for example patients with newly diagnosed T2DM, may be beneficial.

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Chapter 3

The lipid profile and mortality risk in elderly type 2 diabetic patients: a ten-year follow-up study (ZODIAC-13)

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Abstract

Background: The precise relationship between the lipid profile and mortality in elderly patients with type 2 diabetes mellitus (T2DM) remains unclear. The aim of this study was to investigate the relationship between the lipid profile over time, and mortality in elderly patients with T2DM.

Methods and findings: In 1998, 881 primary care patients with T2DM aged 60 years and older participated in the ZODIAC study, a prospective observational study. The cohort was divided into two age categories: 60-75 years and older than 75 years. Updated means of all lipid profile indices were calculated after a median follow-up time of 9.8 years. These values were used as time dependent covariates in a Cox proportional hazard model. The cholesterol-HDL ratio and LDL-cholesterol were positively related to both all-cause and cardiovascular mortality in the low age group. In contrast, except for the triglyceride level, none of the other lipid profile indices were related to all-cause mortality in patients aged over 75 years. The mortality risk decreased by 17% (95%CI: 5% to 27%) for each 1 mmol/L higher serum level of triglycerides. The relationships between the various lipid profile indices and cardiovascular mortality were not significant. However, the results were different after stratification for diabetes duration. In the subgroup of elderly patients with a diabetes duration of 8 years and longer, higher lipids were predictive of increased cardiovascular mortality. The main limitation of this study is its observational design, which prevents us drawing conclusions about causality.

Conclusion: Although the lipid profile was not predictive in the overall group of elderly patients, higher lipids were related to increased cardiovascular mortality in patients with diabetes of long duration. In order to make valid recommendations concerning lipid-lowering treatment, a randomized controlled trial or a meta-analysis concerning this specific population is mandatory.

Introduction

Type 2 diabetes mellitus (T2DM) and dyslipidemia are important risk factors for cardiovascular disease [1,2]. Randomized controlled trials have clearly demonstrated the positive effects of lipid-lowering treatment (LLT) in T2DM, as shown in two recent meta-analyses [3,4]. Therefore, treatment with lipid-lowering drugs is recommended for virtually all patients with T2DM in the various guidelines [5-7]. Although part of these studies included patients older than 75 years, no separate analyses were performed for this age group. The only randomized controlled trial specifically designed for the elderly (70-82 years) showed a reduction in cardiovascular disease risk [8]. This reduction was largely attributable to positive effects in the secondary prevention group, as shown in a post-hoc analysis. The risk of cardiovascular disease was not reduced in patients with a history of diabetes, although the number of patients with diabetes was probably too small to permit accurate interpretation of the treatment effect [8]. Based on the current evidence, the question therefore remains whether there is a benefit of lowering lipids in the elderly diabetic population. This especially holds true for primary prevention. Also, in a cohort of patients form the general population without verified coronary heart disease, higher cholesterol levels were not related to an increased risk of coronary heart disease [9]. Some other longitudinal studies, including the Framingham study, have even observed increased all-cause mortality rates with lower total cholesterol levels in the general elderly population, regardless of the diabetes status [10-14]. We aimed to explore the association between the lipid profile and the risk of mortality in a prospectively designed cohort study of elderly T2DM patients.

Methods

This study is part of the ZODIAC (Zwolle Outpatient Diabetes project Integrating Available Care) study; the design and details of which have been presented elsewhere [15]. In this study, general practitioners are assisted by hospital-based nurses specialized in diabetes in their care of patients with T2DM. In the first year (1998) of the study, 1664 patients were assessed for eligibility, and a total of 1143 patients agreed to participate in the study (see flow diagram in figure 1). For the present study, we selected all patients aged 60 years and older (n=881). Baseline data consisted of a full medical history including macrovascular complications, medication use, and tobacco consumption. Laboratory and physical assessment data, such as lipid profile, serum creatinine levels, the urinary albumin-to-creatinine ratio, blood pressure, weight, and height were collected annually. Total cholesterol, HDL-cholesterol as well as the triglyceride level were determined using standard hospital procedures. LDL-cholesterol was calculated using the Friedewald equation [16]. Patients were not specifically instructed to collect a fasting lipid profile at that time. Early 2009, the life status and cause of death were retrieved from records maintained by the hospital and the general practitioners.

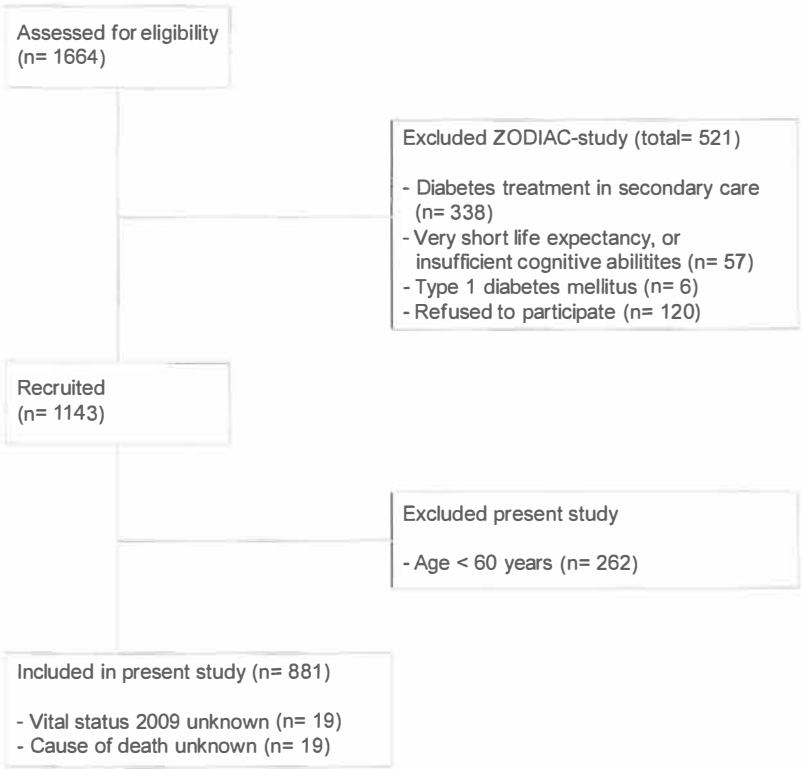

Figure 1. Flow diagram showing the selection process of the ZODIAC and the present study.

The cohort of 881 patients was divided into two age groups: 75 years and younger (low age group), and older than 75 years (high age group). Updated means of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, and the cholesterol-HDL ratio were calculated for each individual from baseline to the end of follow-up by averaging the baseline values with the mean annual values. This technique is similar to the one used in the United Kingdom Prospective Diabetes Study (UKPDS) [17]. For example, at one year the updated mean total cholesterol is the average of the baseline and one year values and at three years it is the average of baseline, one year, two year and three year values. Eleven baseline variables were selected as possible confounders in the relationship between the lipid profile indices and mortality: gender, smoking (yes or no), body mass index (BMI), duration of diabetes, serum creatinine level, macrovascular complications (yes or no), albuminuria (yes or no), systolic blood pressure, use of lipid-lowering drugs (yes or no), use of antihypertensive drugs (yes or no), and age. Patients were considered to have macrovascular complications when they had a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke or transient ischaemic attack.

Continuous variables are represented as mean (± standard deviation) for normally distributed values and as median (interquartile range) for non-normally distributed values. Normality was evaluated using Q-Q plots. Nominal variables are represented as the total number of patients (percentage). A Cox proportional hazard model was used to investigate the relationship between the updated means of the lipid profile indices, as time dependent covariates, and mortality with and without adjustment for the selected confounders. The model was used in both age groups. The assumption of proportional hazards was checked by inspecting the Schoenfeld residual plots for each predictor variable. No substantial deviations from the plots were observed. Low cholesterol levels seen in patients close to death can influence the relationship between the lipid profile and mortality. Therefore, we performed additional analyses in which we excluded the deaths occurring in the first 4 years of follow-up. Analyses were repeated in strata according to diabetes duration. The diabetes duration variable was categorised into two different groups: diabetes of short duration (below the median value) and diabetes of long duration (the median value and higher). All analyses were performed with SPSS version 15.0.1 (SPSS inc., Chicago, Illinois, USA).

Ethics statement

The ZODIAC study and the informed consent procedure was approved by the local medical ethics committee of the Isala Clinics, Zwolle, The Netherlands. Verbal informed consent was obtained for all patients by the participating diabetes specialist nurses and the consent was documented in the patients records. According to Dutch law, written informed consent was not necessary for this type of study in 1998. All data were analyzed anonymously.

Results

The baseline characteristics of the study population are presented in table 1. Diastolic blood pressure, BMI, total cholesterol, level of triglycerides and the proportion of smoking patients were lower in the high age group, whilst HDL-cholesterol and serum creatinine were higher. Also, diabetes duration was longer and complications were more prevalent. There were no differences between groups regarding glycemic control and the proportion of patients on oral glucose lowering agents and insulin treatment. In the entire cohort, 95 patients (11%) received LLT at the beginning of the study. During a median follow-up time of 9.8 years, LLT was started in 171 patients (31%) in the low age group, and in 26 patients (8%) in the high age group. Two hundred sixty-seven out of 326 patients (82%) died in the high age group and 198 out of 555 patients (36%) in the low age group. The proportions of cardiovascular mortality in the high and low age groups were 43% (114 out of 267) and 42% (83 out of 198), respectively.

	60-75 years *n* = 555	> 75 years *n* = 326	p-value
Age (years)	69 (65-72)	80 (77-83)	-
Male sex	230 (41)	118 (36)	0.124
Duration ofT2DM (years)	6 (3-12)	8 (4-13)	0.001
Body mass index (kg/m²)	29.0 (±4.6)	27.7 (±4.4)	<0.001
Systolic blood pressure (mm Hg)	158.2 (±25.1)	156.0 (±24.0)	0.206
Diastolic blood pressure (mm Hg)	84.8 (±11.2)	81.5 (±10.8)	<0.001
Pulse pressure (mm Hg)	73.5 (±20.2)	74.6 (±18.9)	0.424
Total cholesterol (mmol/L)	5.7 (±1.1)	5.5 (±1.2)	0.009
Cholesterol-HDL ratio	5.3 (±1.5)	4.9 (±1.6)	0.001
LDL-cholesterol (mmol/L)	3.4 (±1.0)	3.3 (±1.0)	0.191
HDL-cholesterol (mmol/L)	1.1 (±0.3)	1.2 (±0.4)	0.016
Triglycerides (mmol/L)	2.6 (±1.5)	2.2 (±1.4)	<0.001
HbA1c (%)	7.5 (±1.4)	7.4 (±1.2)	0.205
Smoking	85 (15)	31 (10)	0.014
Albuminuria present	245 (44)	181 (56)	0.002
Macrovascular complications present	208 (37)	149 (46)	0.016
Receiving antihypertensive treatment	277 (50)	197 (60)	0.002
Receiving lipid-lowering treatment	80 (14)	15 (5)	<0.001
Receiving oral glucose lowering agents	406 (73)	234 (72)	0.659
Receiving insulin treatment	94 (17)	66 (20)	0.219
Serum creatinine (umol/L)	92 (82-104)	98 (86-117)	<0.001

Table 1. Baseline characteristics. Data are means (± SD), medians (interquartile range) or *n* (%). Chi-squared tests were used for categorical variables and independent t-tests or Mann-Whitney U tests, where appropriate, for continuous variables.

Low age group

Figure 2 presents the hazard ratios, adjusted for the selected confounders, for all-cause and cardiovascular mortality in both age groups. An increase of the cholesterol-HDL ratio, as well as increased levels of LDL-cholesterol were associated with both increased all-cause and cardiovascular mortality in the low age group. An increase of 1 mmol/L in the level of LDL-cholesterol led to an increase of the hazard of cardiovascular mortality by 49% (95% confidence interval (CI) 17% to 91%). There was a non-significant positive relationship between total cholesterol and all-cause as well as cardiovascular mortality. The relationships for both HDL-cholesterol and triglycerides with mortality were also non-significant.

High age group

Except for the triglyceride level, none of the other lipid profile indices were related to all-cause mortality in the high age group. The mortality risk decreased by 17% (95%CI 5% to 27%) for each 1 mmol/L higher level of triglycerides. All associations between the lipid profile indices and cardiovascular mortality were non-significant.

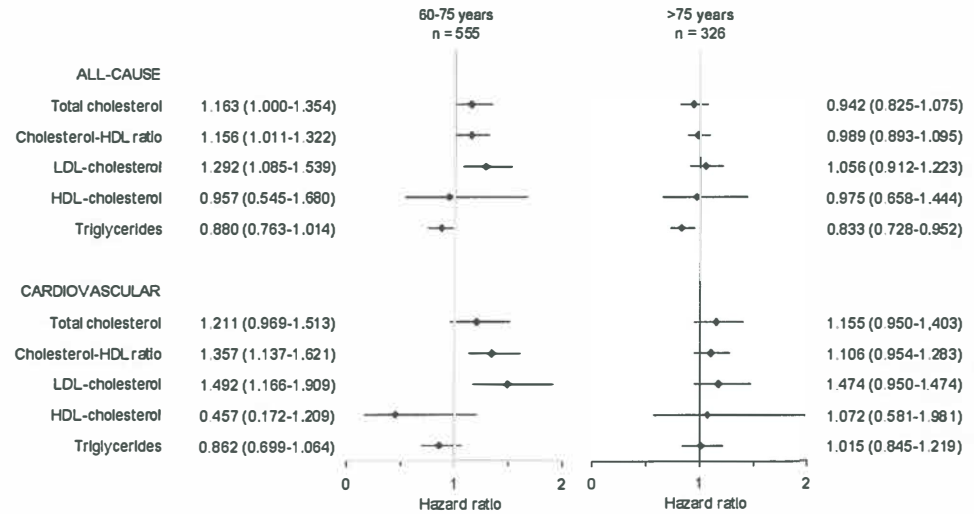

Figure 2. Combined forest plot: lipid profile and mortality. Hazard ratios and the 95% confidence intervals of the various lipid profile indices for all-cause and cardiovascular mortality in both age groups, adjusted for the selected confounders.

Exclusion of early mortality

After exclusion of the deaths in the first years of follow-up the relationship between LDL-cholesterol and mortality became more pronounced in the low age group, but did not relevantly change in the group of the elderly diabetic patients (figure 3).

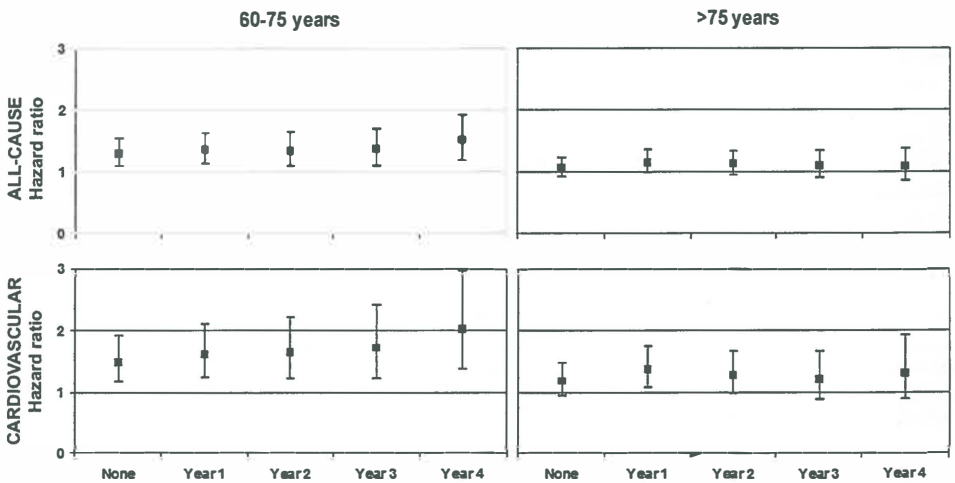

Figure 3. Exclusion of early mortality. Hazard ratios and their 95% confidence intervals (adjusted for confounders) of LDL-cholesterol for all-cause and cardiovascular mortality after exclusion of the deaths in the first follow-up years. Hazard ratios of several analyses in both age groups are presented: an analysis including all follow-up years, an analysis in which the first year of follow-up was excluded, an analysis in which the first two years of follow-up was excluded and so forth.

The same effect was also seen regarding total cholesterol (data not shown). All other associations, including the one between triglycerides and all-cause mortality, did not relevantly change after exclusion of early mortality.

Diabetes duration

When the analyses were repeated in strata according to diabetes duration, the results differed from the overall results (figure 4). For patients in the low age group with diabetes of long duration (≥ 6 years), the cholesterol-HDL ratio and LDL-cholesterol were positively associated with both all-cause and cardiovascular mortality. HDL-cholesterol was inversely related to cardiovascular mortality in this group. Only the triglyceride level was related to all-cause mortality for patients in the low age group with diabetes of short duration: this relationship was inverse.

The lipid profile was not predictive of all-cause mortality in the high age group, regardless of diabetes duration. An increase of the cholesterol-HDL ratio, as well as increased levels of total and LDL-cholesterol were associated with increased cardiovascular mortality in elderly patients with diabetes of long duration (≥ 8 years).

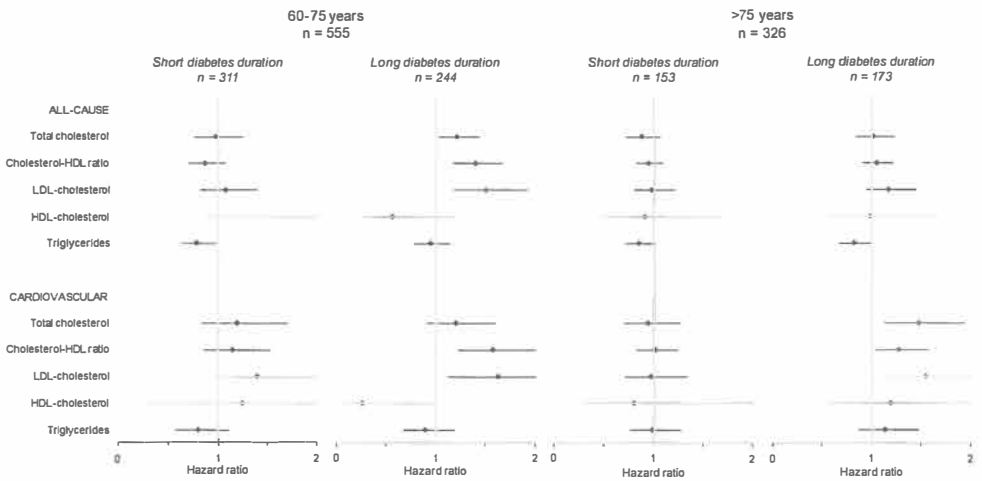

Figure 4. Combined forest plot: short versus long diabetes duration. Hazard ratios and the 95% confidence intervals of the various lipid profile indices stratified for diabetes duration (< median value versus median value and higher), adjusted for the selected confounders.

Discussion

After a median follow-up time of almost 10 years, the overall results showed that higher lipid levels were unrelated to increased all-cause and cardiovascular mortality in patients with T2DM aged over 75 years. However, the results were different when stratified for diabetes duration. In elderly patients with a diabetes duration of 8 years or longer, higher lipids were related to increased cardiovascular mortality. The overall results showed an inverse relationship between the triglyceride level and all-cause mortality in the high age group. An increase of 1 mmol/L led to a decrease in mortality risk of 17%. In younger patients we found relations as one would expect, e.g. a higher LDL-cholesterol is related to increased mortality.

With increasing age, age itself becomes more important in the prediction of mortality. As a consequence, the predictive value of other risk factors like lipid profile abnormalities becomes smaller. Interestingly, in the high age group we only found positive relationships in patients with diabetes of long duration. These results correspond with a previous study that showed that patients with middle age- and elderly onset diabetes appear to represent distinct groups with differing burdens of disease [18]. One could hypothesize that patients with diabetes of long duration may represent a selected group with a worse cardiovascular risk profile compared to patients with diabetes of short duration. So, the predictive value of the lipid profile may be higher in patients with diabetes of long duration, because the total cardiovascular mortality risk in this group may be higher. However, this hypothesis could not be confirmed in our cohort: the proportions of cardiovascular mortality for the elderly patients with diabetes of short and long duration were 47% and 54%, respectively (p=0.907).

Low total cholesterol has been described before as a marker of increased mortality in the general elderly population [10-14]. We found an inverse relationship between the triglyceride level and all-cause mortality in both the total group of patients older than 75 years, and in a subgroup of younger patients with diabetes of short duration. Various explanations have been proposed for the absence of a positive relationship and sometimes an inverse relationship, between lipids and mortality. Lower cholesterol levels may represent occult disease or may be a signal of declining health [13]. It is also possible that subjects surviving long enough with a higher cholesterol are less susceptible to the adverse consequences of dyslipidemia; those individuals susceptible to the effects of high cholesterol will probably die before reaching the age of 75 years. Those individuals who survive, represent a selected group with lower cholesterol levels and with a genetic makeup or other factors protecting them from the effects of higher cholesterol levels [12]. To adjust for the possible confounding effects of co-morbidity and frailty, we performed additional analyses in which we excluded deaths occurring in the first years of follow-up. The relationship between the triglyceride level and all-cause mortality

remained inverse. All other lipid profile indices remained non-predictive of mortality in the high age group.

In very old people from the general population with no history of cardiovascular disease, classic risk factors included in the Framingham risk score did not predict cardiovascular mortality [19]. This study and the previously mentioned studies, that showed an inverse relationship between cholesterol and mortality, question the ability of lipid profile abnormalities to identify elderly patients at high risk of (cardiovascular) mortality [10-14,19]. It seems therefore that classic risk factors may have different consequences when assessed in elderly patients. However, it is important to emphasize that older adults exhibit widely heterogeneous health status, ranging from healthy to frail [20,21]. In a guideline for improving diabetes care in older adults, it has been suggested to treat lipid profile abnormalities only after overall health status has been considered [20]. Furthermore, it was stated that only 2 to 3 years are required to see benefits from LLT [20]. Physicians caring for elderly diabetic patients should take co-morbidity and the estimated life expectancy into account when setting treatment goals for the individual patient. In our opinion, it is plausible that there are specific groups in which lipids are predictive of mortality and LLT is beneficial; perhaps in elderly patients with diabetes of long duration.

The proportion of patients receiving LLT at the start of the ZODIAC-study was small in both age categories. As a consequence, it was not possible to perform separate analyses for the effects of LLT on mortality. One has to remember that this study started in 1998, and the treatment goals for the lipid profile in patients with T2DM are more stringent nowadays. Whether LLT is beneficial in elderly patients with T2DM remains unanswered in this study. Several trials have investigated the effects of statins in patients with T2DM. One large randomized controlled trial, including 5963 diabetic patients, showed beneficial effect of LLT on major vascular events in elderly T2DM patients (≥ 65 years) [22]. Furthermore, a meta-analysis investigating the effects of LLT in diabetic patients also performed a separate analysis for patients aged 65 years and older [4]. The relative risk for major vascular events was 0.81 (95%CI 0.71 to 0.92) in favor of LLT. Again, only a few studies had included patients aged over 75 years.

The main limitation of this study is its observational design, which prevents us drawing conclusions about causality. Another limitation is that we are not informed about the proportion of non-fasting lipid profiles during the yearly assessments in our study population. However, a fasting blood sample is not necessary for a reliable measurement of total cholesterol and HDL-cholesterol.

Our study also has notable strengths. Firstly, we used the various lipid profile indices as time dependent covariates and by means of this analysis we corrected for changes over time.

Secondly, with a median follow-up of almost 10 years, we were able to observe a substantial number of deaths to base our conclusions on.

To our knowledge this is the first prospective observational study which specifically investigated the relationship between lipids and mortality in a cohort of T2DM patients older than 75 years. Although the lipid profile was not predictive in the overall group of elderly patients, higher lipids were related to increased cardiovascular mortality in patients with diabetes of long duration. So, it may be necessary to formulate different treatment goals for different patients groups. In order to identify these specific groups and to make valid recommendations concerning LLT, a randomized controlled trial or a meta-analysis concerning this specific population is mandatory.

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Chapter 4

Lower blood pressure associated with higher mortality in elderly diabetic patients (ZODIAC-12)

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Abstract

Objective: To investigate the relationship between blood pressure over time, and mortality in elderly patients with type 2 diabetes mellitus (T2DM).

Design: Prospective observational cohort study.

Setting: Primary care, Zwolle, The Netherlands.

Subjects: Patients with T2DM aged 60 years and older (n=881). The cohort was divided into two age categories: 60-75 years and older than 75 years.

Methods: Updated means for systolic, diastolic and pulse pressures were calculated after a median follow-up time of 9.8 years. These values were used as time dependent covariates in a Cox proportional hazard model. Main outcome measures were all-cause and cardiovascular mortality.

Results: All of the blood pressure measures were inversely related to all-cause mortality in elderly diabetic patients (>75 years). Furthermore, these relationships were specifically found in elderly patients treated with antihypertensive medication at baseline. A decrease of 10 mm Hg in systolic blood pressure, diastolic blood pressure, and pulse pressure led to a mortality increase of 22% [95%CI: 13-31%], 30% [95%CI: 13%-46%] and 22% [95%CI: 11%-33%] respectively. In the low age group (60-75 years) no relationship was found between blood pressure and mortality.

Conclusions: Blood pressure is a marker for mortality in elderly T2DM patients, however the relationship is inverse.

Introduction

Hypertension increases the already high risk for cardiovascular disease in patients with type 2 diabetes mellitus (T2DM) [1,2]. Although many large randomised controlled trials have shown that blood pressure control is beneficial for patients with T2DM, the level of evidence for aggressive treatment as recommended by the various international guidelines is low [3-5]. Recent studies have shown that targeting for a systolic blood pressure lower than the standard target (<140 mm Hg) does not provide additional benefit [6-8].

Aggressive treatment is even more controversial in old age, since several epidemiological population studies and one meta-analysis of randomised controlled trials suggest an inverse relationship between mortality risk and blood pressure in elderly subjects from the general population [9-16]. Although a few hypertension trials included patients older than 75 years, no separate analyses were performed for this age group. A recent study has shown that in patients over the age of 80 without heart failure for whom antihypertensive therapy was considered indicated, a reduction in blood pressure resulted in improved cardiovascular morbidity as well as cardiovascular and all-cause mortality [17]. However, this study included healthy elderly patients and only a small subgroup of patients with T2DM. As a consequence, data from this study can not be generalized to elderly diabetic patients who have higher rates of functional disability and coexisting illnesses than those without T2DM [18,19].

To our knowledge, the relationship between blood pressure and mortality in (elderly) diabetic patients has been described only once before in a cohort study from Finland in which an inverse relationship was reported [20]. To add to the body of evidence, we analysed the all-cause and cardiovascular mortality risk in association with blood pressure and pulse pressure over time in a cohort of elderly diabetic patients.

Methods

This study is part of the ZODIAC (Zwolle Outpatient Diabetes project Integrating Available Care) study; the design and details of which have been presented elsewhere [21]. In this project, general practitioners are assisted by hospital-based nurses specialised in diabetes in their care of patients with T2DM. The patients consult with the nurses once per year. In the first year (1998) of the ZODIAC study, 1664 patients were assessed for eligibility. A total of 338 patients were already treated in the secondary care for their diabetes. Another 57 patients were excluded because of a very short life expectancy (including patients with active cancer) or insufficient cognitive abilities. Eventually, 1269 eligible patients were invited to participate. Of those, 1143 patients agreed to participate in the study. For the present study, we selected all

patients aged 60 years and older (n = 881). Baseline data, collected in 1998 and 1999, consisted of a full medical history including macrovascular complications, medication use, and tobacco consumption. Laboratory and physical assessment data, such as lipid profile, creatinine levels, the presence of albuminuria, blood pressure, weight, and height were collected annually. Blood pressure was measured twice with a Welch Allyn Sphygmomanometer in the supine position after at least five minutes of rest. For each visit the mean blood pressure of two recordings was calculated. Early 2009, the life status and cause of death were retrieved from records maintained by the hospital and the general practitioners.

The cohort of 881 patients was divided into two age groups: 60-75 years (low age group) and older than 75 years (high age group). Updated means for systolic blood pressure, diastolic blood pressure, and pulse pressure were calculated for each individual from baseline to the end of follow-up by averaging the baseline values with the mean annual values. This technique is similar to the one used in the United Kingdom Prospective Diabetes Study (UKPDS) [22]. For example, at two years the updated mean of systolic blood pressure is the average of baseline, one year and two year values. Eleven baseline variables were selected for their possible confounding effects on the relationship between blood pressure and mortality: gender, smoking (yes or no), body mass index, duration of diabetes, serum creatinine level, cholesterol-HDL ratio, macrovascular complications (yes or no), albuminuria (yes or no), the use of lipid lowering and antihypertensive medications (yes or no), and age. Patients were considered to have macrovascular complications when they had a previous history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, or transient ischaemic attack.

Continuous variables are represented as a mean (± standard deviation) for the normally distributed values and as a median (interquartile range) for the non-normally distributed values. Normality was evaluated using Q-Q plots and histograms. Nominal variables are represented as total number (percentage). A Cox proportional hazard model was used to investigate the relationship between the updated means of the different blood pressure measures, as time dependent covariates, and mortality with adjustment for the selected confounders. The model was used for both age groups. Analyses were repeated in strata according to the baseline use of antihypertensive medication (yes or no). All hazard ratios (HRs) refer to a pressure increase of 10 mm Hg. For Kaplan-Meier curves, the baseline systolic blood pressure values were categorized into three different groups (< 140 mm Hg, 140-169 mm Hg and ≥ 170 mm Hg). The assumption of proportional hazards was checked by inspecting the Schoenfeld residual plots for the baseline predictor variables and the log(-log(S(t)) plots for different categories of the baseline predictors. No substantial deviations from the plots were observed. All analyses were performed with SPSS version 15.0.1 software (SPSS inc., Chicago, Illinois, USA) and Stata version 10 (StataCorp, College Station, Texas, USA).

Ethics statement

The ZODIAC study and the informed consent procedure was approved by the local medical ethics committee of the Isala Clinics, Zwolle, The Netherlands. Verbal informed consent was obtained for all patients by the participating diabetes specialist nurses and the consent was documented in the patients records. According to Dutch law, written informed consent was not necessary for this type of study in 1998. All data were analysed anonymously.

Results

The baseline characteristics of the study population are shown in table 1. The median age [interquartile range] at baseline was 80 years [77-83] in the high age group (>75 years) and 69 [65-72] in the low age group (60-75 years). During a median follow-up time of 9.8 years, 267 patients (81.9%) in the high age group and 198 patients (35.7%) in the low age group had died. Cause of death was not known for 19 patients (2.2%), and 19 patients were lost to follow-up (2.2%). The proportion of deaths attributable to cardiovascular factors was 42.7% in the high age group and 41.9% in the low age group. In the high age group, the mortality rate for patients with a systolic blood pressure < 140 mm Hg was 89.7% compared to 76.9% in the group with a blood pressure ≥ 170 mm Hg (figure 1). In the low age groups these proportions were 37.0% and 39.6%, respectively.

	60-75 years *n = 555*	**> 75 years** *n = 326*
Age (years)	69 (65-72)	80 (77-83)
Male sex	230 (41%)	118 (36%)
Body mass index (kg/m2)	29.0 (4.6)	27.7 (4.4)
Systolic blood pressure (mm Hg)	158.2 (25.1)	156.0 (24.0)
Diastolic blood pressure (mm Hg)	84.8 (11.2)	81.5 (10.8)
Pulse pressure (mm Hg)	73.5 (20.2)	74.6 (18.9)
Current smoking	85 (15%)	31 (10%)
Albuminuria present	245 (44%)	181 (56%)
Cholesterol-HDL ratio	5.3 (1.5)	4.9 (1.6)
HbA1c (%)	7.5 (1.4)	7.4 (1.2)
Macrovascular complications present	208 (37%)	149 (46%)
Receiving antihypertensive treatment	277 (50%)	197 (60%)
- ACE-inhibitor	128 (23.1%)	84 (25.8%)
- Beta-blocker	119 (21.4%)	59 (18.1%)
Receiving lipid lowering treatment	80 (14%)	15 (5%)
Duration ofT2DM (years)	6 (3-12)	8 (4-13)
Serum creatinine (umol/L)	92 (82-104)	98 (86-117)

Table 1. Baseline characteristics. Data are means (± SD), medians (interquartile range) or n (%).

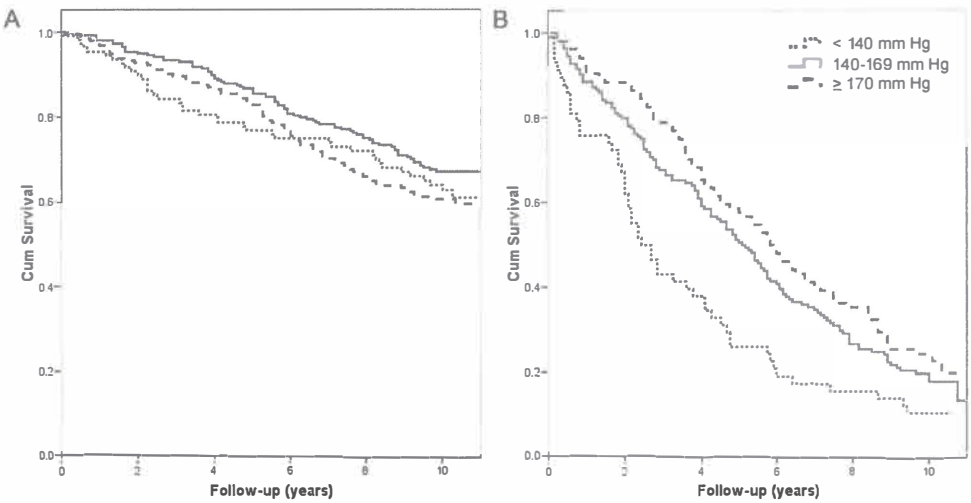

Figure 1. Kaplan-Meier curve; systolic blood pressure and all-cause mortality in both the low (A) and high (B) age groups.

All-cause and cardiovascular mortality

Table 2 presents the HRs for systolic blood pressure, diastolic blood pressure, and pulse pressure for all-cause and cardiovascular mortality. The updated means for all blood pressure measures in the high age group were inversely related to all-cause mortality. After adjusting for confounders, the mortality risk increased by 16% [95% CI: 9-23%] and 24% [95% CI: 11-38%] for every 10 mm Hg decrease in systolic and diastolic pressures respectively. The mortality risk was 16% [95% CI: 7-25%] higher per 10 mm Hg decrease in pulse pressure after adjusting for the selected confounders. There was no significant relationship between cardiovascular mortality and blood pressure in the high age group. In the low age group the associations between blood pressure and mortality, both all-cause and cardiovascular mortality, were also not significant.

Baseline use of antihypertensive medication

After adjusting for confounders, systolic blood pressure was inversely related to both all-cause and cardiovascular mortality in the group of elderly patients (>75 years) who received antihypertensive medication at baseline (HR all-cause 0.78 [95% CI: 0.69-0.87], HR cardiovascular 0.85 [95% CI: 0.72-0.98]). For elderly patients, who did not use antihypertensive medication, the HRs were 0.95 [95% CI: 0.83-1.08] and 1.02 [95% CI: 0.83-1.21] for all-cause and cardiovascular mortality, respectively. For diastolic blood pressure and pulse pressure the results were comparable: for elderly patients who received antihypertensive medication, the HRs for all-cause mortality were 0.70 [95% CI: 0.54-0.87] and 0.78 [95% CI: 0.67-0.89], respectively.

	60-75 Years		> 75 Years	
	All-cause Mortality	Cardiovascular Mortality	All-cause Mortality	Cardiovascular Mortality
Systolic blood pressure				
Unadjusted for confounders	1.03 (0.95-1.10)	0.95 (0.84-1.07)	0.85 (0.78-0.91)	0.89 (0.80-0.99)
Adjusted for confounders	1.01 (0.93-1.09)	0.92 (0.80-1.05)	0.84 (0.77-0.91)	0.90 (0.79-1.00)
Diastolic blood pressure				
Unadjusted for confounders	0.94 (0.78-1.11)	0.83 (0.58-1.08)	0.71 (0.58-0.85)	0.86 (0.66-1.07)
Adjusted for confounders	1.04 (0.88-1.21)	0.90 (0.65-1.16)	0.76 (0.62-0.89)	0.91 (0.70-1.12)
Pulse pressure				
Unadjusted for confounders	1.06 (0.97-1.16)	0.98 (0.84-1.13)	0.85 (0.77-0.93)	0.88 (0.76-1.00)
Adjusted for confounders	1.00 (0.89-1.10)	0.91 (0.75-1.07)	0.84 (0.75-0.93)	0.87 (0.74-1.01)

Table 2. Hazard ratios for all-cause and cardiovascular mortality. The hazard ratios (95% confidence interval) refer to a pressure increase of 10 mm Hg. Gender, smoking (yes or no), body mass index, duration of diabetes, serum creatinine level, cholesterol-HDL ratio, macrovascular complications (yes or no), albuminuria (yes or no), the use of lipid lowering and antihypertensive medications (yes or no), and age were selected as potential confounders.

Low blood pressure before death

Low blood pressure seen in patients close to death could account for the inverse relationship between blood pressure and mortality in our group of elderly patients. To examine this, we performed an additional analysis in which we excluded the deaths early in follow-up and an analysis in which we excluded the last blood pressure value before death. The relationships between blood pressure and mortality in these analyses did not relevantly change (data not shown).

Discussion

In this prospective observational study, lower blood pressure was related to higher all-cause and cardiovascular mortality rates in elderly T2DM patients (>75 years) who were using antihypertensive medication at baseline. A decrease of 10 mm Hg in systolic blood pressure, diastolic blood pressure, and pulse pressure was associated with an increase in mortality risk of 22%, 30%, and 22% respectively. Remarkably, these relationships did not exist in the elderly patients who did not receive antihypertensive treatment at baseline. We also observed another important finding: there was no relationship between blood pressure and mortality in the low age group (60-75 years).

A recent meta-analysis showed that the all-cause mortality risk is not reduced by hypertension treatment in very elderly patients from the general population [23]. Furthermore, several epidemiological studies have described an inverse relationship between blood pressure and mortality in elderly subjects [10-16]. To our knowledge, only the study by Rönnback et al. showed such an inverse relationship in elderly diabetic patients [20]. Where this study used the baseline blood pressure values in their analyses, we used the different measures of blood pressure as time dependent covariates. This allowed us to correct for changes in blood pressure over time and even, to some extent, for the imprecision inherent to a single blood pressure measurement. Rönnback et al. selected patients in primary care using a single selection criterion: T2DM, as did we. As a result, both of these study populations are more representative of typical type 2 diabetic patients than the populations studied in other hypertension trials.

It is important to emphasize that the associations found between blood pressure and mortality do not imply causality. Because of the observational nature of our study we can only speculate about the underlying mechanisms. However, it is interesting to generate hypotheses about the role of antihypertensive medication. There are many possible explanations why the inverse relationship was only found for elderly patients treated with antihypertensive medication at baseline. Firstly, excessive lowering of diastolic blood pressure could play a role. In the Systolic Hypertension in the Elderly Program (SHEP) a decrease of diastolic blood pressure in the active treatment group was related to an increased risk of cardiovascular disease [24]. More recently, results of the International Verapamil SR-trandolapril (INVEST) trial showed that a systolic blood pressure below 115 mm Hg was associated with increased mortality [7].

Secondly, side effects of antihypertensive medication may be a possible confounder. For example orthostatic hypotension, a possible manifestation of autonomic neuropathy, has been described as an independent predictor of all-cause mortality [25]. Its prevalence increases with age; moreover, it is more prevalent in patients with diabetes [26,27]. Because data on orthostatic hypotension have not been collected in our study, we can only hypothesize about its possible effect.

Thirdly, the existing co-morbidities and the general frailty of elderly patients have been suggested as the explanation for the inverse relationship between blood pressure and mortality in elderly patients in the general population [28]. One could hypothesize that congestive heart failure causes the inverse relationship in our study. Patients with heart failure tend to have lower blood pressure values, and perhaps the prevalence of heart failure in our study cohort was higher in the patients using antihypertensives at baseline. Both cardiovascular disease and diabetes mellitus are important risk factors for the development of heart failure [29]. In our model, we included previous macrovascular complications as a covariate. Furthermore,

when we excluded the last blood pressure value before death and the data associated with the initial deaths in our study, the results were not different. Therefore it is less plausible that co-morbidity (e.g. heart failure) or frailty are the only explanations for the inverse relationship observed.

The above mentioned explanations for the inverse relationship in the high age group, may also account for the absence of a relationship in the low age group. However, many large randomised controlled trials have included diabetic patients aged 60-75 years. Data from these trials have been reviewed in a meta-analysis, which showed beneficial effects of hypertension treatment [30]. In our opinion, it is more likely that our findings are a result of the lower mortality rate in this age group, which prevents us from drawing definite conclusions.

Our main challenge is to identify the applicability of our results into daily practice. Although no causality was proven or implied for this observational relationship, these results do raise questions about the necessity for aggressive treatment of hypertension in elderly diabetic patients; moreover, they are highly suggestive that hypertension treatment is harmful. This study and data from recent studies indicate that there is no evidence for the ever decreasing target value for systolic blood pressure in both elderly and diabetic patients [6-8, 23].

We are not recommending against the initiation of antihypertensive treatment in elderly diabetic patients. Nevertheless, we need to realize that elderly patients exhibit widely heterogeneous health status, ranging form healthy to frail [18]. Physicians caring for elderly diabetic patients should take co-morbidity and the estimated life expectancy into account when setting treatment goals for the individual patient. In order to make valid recommendations concerning the treatment of hypertension in elderly patients with T2DM and the optimum target level for blood pressure, a randomised controlled trial or a meta-analysis concerning this specific population is necessary.

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Chapter 5

The midregional fragment of pro-A-type natriuretic peptide, blood pressure and mortality in a prospective cohort of patients with type 2 diabetes (ZODIAC-25)

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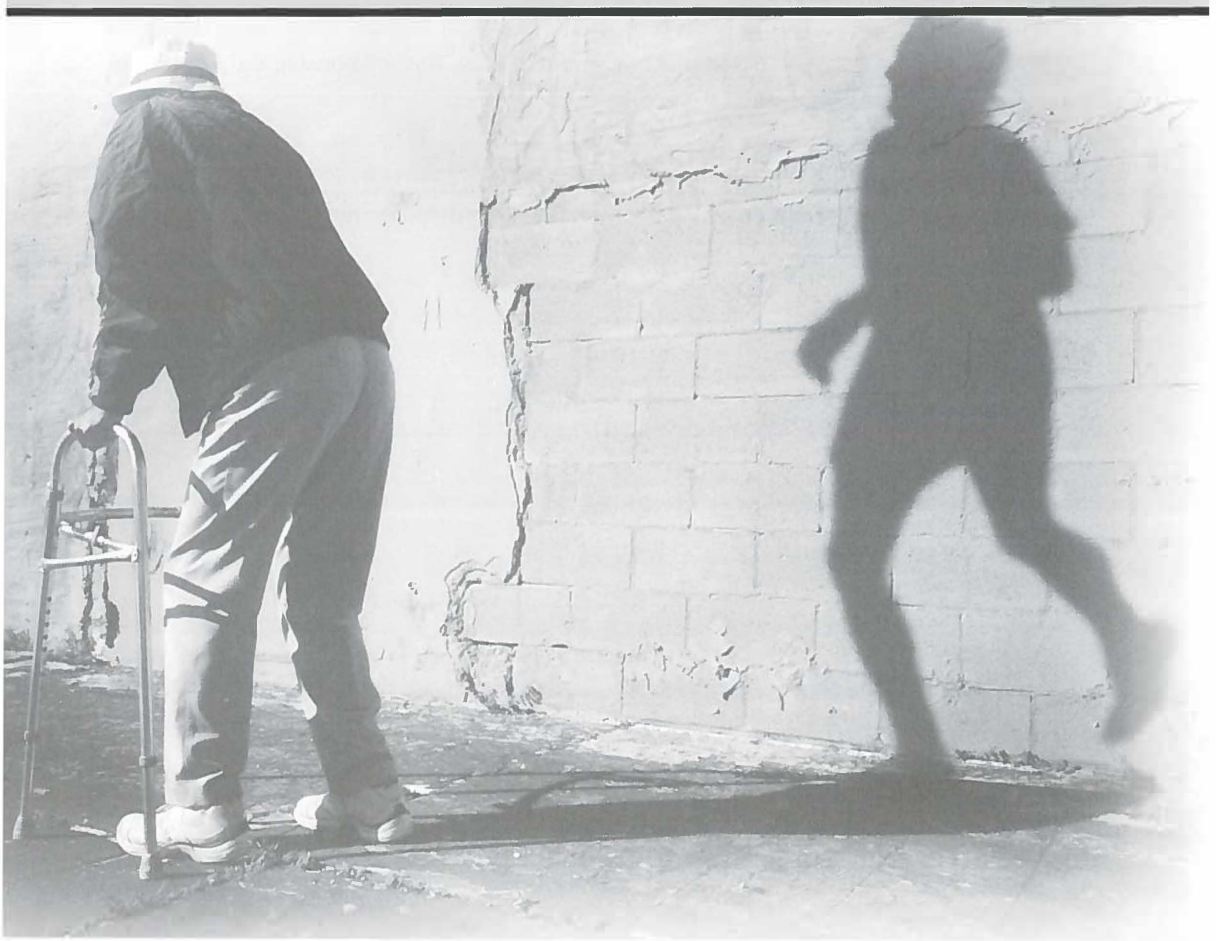

Abstract

Objective: Evidence that MR-proANP is a marker of mortality in patients with type 2 diabetes is limited. Therefore, we aimed to investigate the capabilities of MR-proANP in predicting mortality. We also investigated whether MR-proANP influences the relationship between blood pressure and mortality in old age.

Research Design and Methods: In 1998, 1143 primary care patients with type 2 diabetes participated in the ZODIAC study. Since blood was drawn for 867 patients (76%), and confounders were missing in 19 patients, the final study sample comprised of 848 patients. After a follow-up time of 10 years, we used Cox proportional hazard models to evaluate the relationship between MR-proANP and (cardiovascular) mortality. Harrell's C statistic was used to compare models with and without MR-proANP. The regression analyses were repeated without MR-proANP for patients aged >75 years.

Results: Median MR-proANP in the total study sample was 75 pmol/L (interquartile range 48-124 pmol/L). During follow-up, 354 (42%) out of 848 patients had died, of which 152 (43%) were attributable to cardiovascular factors. MR-proANP was independently associated with all-cause and cardiovascular mortality, irrespective of age. In old age, there was a significant inverse relationship between blood pressure and mortality. This relationship did not change after adjustment for MR-proANP.

Conclusions: MR-proANP is independently associated with mortality in patients with type 2 diabetes. MR-proANP did not influence the inverse relationship between blood pressure and mortality in elderly patients.

Introduction

Natriuretic peptides are important cardiac hormones that have both diagnostic and prognostic value in patients with heart failure [1,2]. A- and B-type natriuretic peptides (ANP and BNP) are derivates of precursor hormones, which are split into the biologically active peptides (ANP and BNP) as well as the biologically inactive N-terminal fragments (NT-proANP and NT-proBNP). Because of variable accessibility and fragmentation of the detected antigen, assays for NT-proANP have performed disappointingly [3,4]. A novel immunoassay has been developed that measures a more stable fragment of proANP, the midregional fragment of proANP (MR-proANP).

Although there are conflicting results with respect to the value of biomarkers, there is still great interest in developing new assays, including MR-proANP, in order to optimise identifying those patients at increased risk of developing cardiovascular complications [5]. Head-to-head comparisons between MR-proANP and NT-proBNP have shown that both peptides are comparable in predicting cardiovascular events and mortality, and in diagnosing heart failure [6-9]. Among patients with chronic heart failure, measurement of MR-proANP even provided prognostic information with respect to mortality independent of NT-proBNP [10,11], There is only one study that has specifically investigated MR-proANP in a cohort of patients with type 2 diabetes [12]. This study showed that higher serum levels of MR-proANP were related to the composite endpoint of cardiovascular events and deaths. Since heart failure is highly prevalent in patients with type 2 diabetes and its prevalence increases with advancing age [13], one may hypothesize that MR-proANP is an important risk factor in elderly patients with type 2 diabetes. Lower prognostic properties of traditional cardiovascular risk factors in elderly (>75 years) patients, compared to younger ones [14-18], underline the importance of finding new cardiovascular risk factors in this specific population.

In a previous study of our group, we found that blood pressure was inversely related to mortality in type 2 diabetic patients aged older than 75 years [17]. We hypothesized that heart failure may be a possible explanation for the inverse relationship. The primary goal of the present study was to investigate the relationship between MR-proANP and mortality in patients with type 2 diabetes, with a special focus on the oldest elderly. We also investigated whether adjustment for MR-proANP, as a measure of heart failure, influenced the inverse relationship of blood pressure with mortality in elderly patients with type 2 diabetes, as published in our ZODIAC-12 study [17].

Research Design and Methods

Study sample

This study is part of the ZODIAC (Zwolle Outpatient Diabetes project Integrating Available Care) study; the design and details of which have been presented elsewhere [19]. In this project, general practitioners are assisted by hospital-based nurses specialized in diabetes in their care of patients with type 2 diabetes. The patients consult with the nurses once per year. In the first year (1998) of the ZODIAC study, 1664 patients were assessed for eligibility. A total of 338 patients that were already treated in the secondary care for their diabetes were excluded from participation. Another 57 patients were excluded because of a very short life expectancy (including patients with active cancer) or insufficient cognitive abilities. Eventually, 1269 eligible patients were invited to participate. Of those, 1143 patients agreed to participate in the study.

Data collection

Baseline data, collected in 1998, consisted of a full medical history including macrovascular complications, medication use, and tobacco consumption. Patients were considered to have macrovascular complications when they had a previous history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, or transient ischaemic attack. Laboratory and physical assessment data, such as lipid profile, creatinine levels, urinary albumin-creatinine ratio, blood pressure, weight, and height were collected annually. Blood pressure was measured twice with a Welch Allyn sphygmomanometer in the supine position after at least five minutes of rest. For each visit the mean blood pressure of two recordings was calculated.

Measure of heart failure

The midregional pro-A-type natriuretic peptide (MR-proANP) was used as a measure of heart failure. Previous studies found that the prognostic properties of MR-proANP are comparable to those of N-terminal pro-B-type natriuretic peptide (NT-proBNP) [6-9]. MR-proANP was measured using an automated sandwich immunoassay, in 867 out of the 1143 (75.9%) patients using plasma collected at baseline and kept frozen at -80 degrees Celsius until analysis according to the instructions of the manufacturer (B·R·A·H·M·S MR-proANP KRYPTOR, B.R.A.H.M.S. GmbH, Hennigsdorf/Berlin, Germany). The limit of quantitation (LOQ) was 4.5 pmol/L. The interassay CV was <6.5% for all MR-proANP concentrations > 10 pmol/L [4].

Clinical endpoints

We examined two clinical endpoints in this study: all-cause and cardiovascular mortality. Early 2009, the vital status and cause of death were retrieved from records maintained by the hospital and the general practitioners. The causes of death were coded according to The International Classification of Diseases, 9th revision (ICD-9).

Statistical analyses

We used SPSS version 16.0 (SAS Insitute, Cary, NC, USA) and STATA version 11 (StataCorp, College Station, Texas USA) for statistical analyses. Continuous variables are represented as mean (± standard deviation) for normally distributed values and as median (interquartile range) for the non-normally distributed variables. Variables with a skewed distribution were logarithmically transformed before analysis. Because of missing confounders in 19 patients, all analyses were performed in 848 out of 867 patients (98%) whose MR-proANP values were determined.

MR-proANP and mortality

Cox proportional hazard models were used to investigate the association between MR-proANP and mortality with adjustment for selected confounders. The following variables were selected for possible confounding effects: age, gender, smoking (dichotomous), body mass index, systolic blood pressure (SBP), duration of diabetes, serum creatinine level, cholesterol-HDL ratio, macrovascular complications (dichotomous), albuminuria (dichotomous), the use of lipid lowering and antihypertensive medications (dichotomous). We used three different models: a crude model, an age- and gender- adjusted model, and a model in which we additionally adjusted for all above mentioned variables. Analyses were performed for MR-proANP as a continuous variable (Log MR-proANP). STATA's ph-test was used to test the assumption of proportional hazards for baseline predictors. All p-values for the ph-test were non-significant, meaning that no substantial deviations were observed. In case of a significant association between MR-proANP and (cardiovascular) mortality, the following analyses were done. Calibration was investigated using the Groennesby and Borgan test, assessing the goodness of fit [20]. Calibration is a measure of how well predicted probabilities agree with actual observed risk. When the average predicted risk within subgroups of a prospective cohort matches the proportion that actually develops disease, the model is considered well calibrated. Harrell's C statistic was used to compare how well the presence of MR-proANP in the different models used, predicts mortality [21]. Harrell's C value is a rank-based measure (more or less comparable with the area under the receiver operating characteristic curve). The higher the value the better the model predicts mortality. Furthermore, the integrated discrimination improvement (IDI) was calculated [22]. The IDI can be interpreted as the difference between model-based probabilities for events and non events for the models with and without MR-proANP.

Blood pressure and mortality

The multivariate model as described above was repeated without MR-proANP for patients aged >75 years in order to investigate whether the relationship between blood pressure and mortality differs between the models with and without MR-proANP. Analyses were performed for MR-proANP as a continuous variable and for MR-proANP as a categorical variable. For the categorical variable, we used a cut-off value of 122 pmol/L. This cut-off value was chosen because in patients with known chronic heart failure, this value had the highest diagnostic accuracy for the detection of a left ventricular ejection fraction <40% [10]. All analyses were performed for SBP, diastolic blood pressure (DBP) and pulse pressure (PP). Additional analyses, in which we used updated mean blood pressure values, were done in order to adjust for changes in blood pressure over time. This technique is similar to the one used in the United Kingdom Prospective Diabetes Study (UKPDS) [23]. For example, at two years the updated mean of SBP is the average of baseline, one year and two year values. The relationship between MR-proANP, blood pressure and mortality was illustrated by using a Kaplan Meier curve, for which all patients were categorised into 4 categories: (1) MR-proANP < median and SBP > median, (2) MR-proANP and SBP < median, (3) MR-proANP and SBP > median, and (4) MR-proANP > median and SBP < median. All hazard ratios (HRs) of the blood pressure indices refer to a pressure increase of 10 mm Hg.

Ethics statement

The ZODIAC study and the informed consent procedure was approved by the local medical ethics committee of the Isala Clinics, Zwolle, The Netherlands. Verbal informed consent was obtained for all patients by the participating diabetes specialist nurses and the consent was documented in the patients' records. According to Dutch law, written informed consent was not necessary for this type of study in 1998. All data were analyzed anonymously.

Results

The baseline characteristics of the study sample are shown in table 1. Median MR-proANP in the total study sample was 75 pmol/L (interquartile range 48-124 pmol/L). For patients >75 years the median MR-proANP value was 122 (80-184) pmol/L. After follow-up for 10 years, 354 out of 848 patients (41.7%) had died. The number of deaths attributable to cardiovascular causes was 152 (42.9%).

	Total *n* = 848	>75 years *n* = 225
Age (years)	70 (60-76)	79 (77-82)
Male sex	366 (43%)	85 (38%)
Body mass index (kg/m²)	29.0 (4.8)	27.8 (4.5)
Systolic blood pressure (mm Hg)	154.6 (24.9)	156.5 (23.1)
Diastolic blood pressure (mm Hg)	84.0 (10.8)	81.8 (10.4)
Pulse pressure (mm Hg)	70.5 (20.1)	74.6 (18.2)
Current smoking	157 (19%)	23 (10%)
Albuminuria present	372 (44%)	122 (54%)
Cholesterol-HDL ratio	5.2 (1.5)	4.8 (1.5)
HbA1c (%)	7.5 (1.3)	7.4 (1.2)
MR-proANP (pmol/L)	75 (48-124)	122 (80-184)
Serum creatinine (umol/L)	92 (81-104)	97 (85-113)
eGFR (MDRD, ml/min/1.73m²)	65 (55-75)	57 (48-67)
Macrovascular complications present	296 (35%)	100 (44%)
Treatment of type 2 diabetes		
- Diet only	92 (11%)	24 (11%)
- Oral glucose lowering agents	607 (72%)	164 (73%)
- Insulin	149 (18%)	37 (16%)
Receiving antihypertensive treatment	415 (49%)	141 (63%)
- ACE-inhibitor	193 (23%)	60 (27%)
- Beta-blocker	161 (19%)	41 (18%)
Receiving lipid lowering treatment	94 (11%)	11 (5%)
Duration of type 2 diabetes (years)	6 (3-11)	8 (4-13)

Table 1. Baseline characteristics. Data are means (± SD), medians (interquartile range) or *n* (%).

Results of the Cox regression analyses for the total study sample as well as the analyses stratified according to age are presented in table 2. In the overall sample and in both age strata, higher levels of Log MR-proANP were related to increased all-cause and cardiovascular mortality. Harrell's C values were the lowest for the patients aged older than 75 years. The highest IDI values and the largest increases in Harrell's C values were observed for adding MR-proANP to the age- and gender adjusted models. Adding MR-proANP to the multivariate model resulted in smaller increases in the Harrell's C values and in lower IDI values. In patients older than 75 years, no significant IDI values were found for cardiovascular mortality.

	HR (95%CI)	Harrell's C (95%CI)	Harrell's C (95%CI) *	IDI, % (95%CI)
Total study sample				
All-cause mortality				
- Model 1	4.16 (3.53-4.91)	0.74 (0.72-0.77)	NA	NA
- Model 2 [a]	2.43 (2.01-2.95)	0.79 (0.77-0.82)	0.77 (0.75-0.79)	4.9 (3.3-6.5)
- Model 3 [b]	2.23 (1.78-2.79)	0.80 (0.78-0.82)	0.79 (0.76-0.81)	2.7 (1.5-3.9)
Cardiovascular mortality				
- Model 1	4.79 (3.73-6.16)	0.76 (0.72-0.80)	NA	NA
- Model 2 [a]	3.29 (2.46-4.40)	0.79 (0.75-0.82)	0.75 (0.71-0.78)	4.6 (2.5-6.7)
- Model 3 [b]	2.42 (1.74-3.38)	0.82 (0.78-0.85)	0.80 (0.77-0.84)	1.2 (0.0-2.4)
Sample ≤ 75 years				
All-cause mortality				
- Model 1	4.14 (3.27-5.25)	0.73 (0.70-0.77)	NA	NA
- Model 2 [a]	2.90 (2.21-3.80)	0.76 (0.73-0.80)	0.73 (0.69-0.77)	6.5 (4.0-8.9)
- Model 3 [b]	2.36 (1.71-3.24)	0.78 (0.74-0.81)	0.76 (0.72-0.80)	2.7 (1.1-4.4)
Cardiovascular mortality				
- Model 1	5.62 (3.98-7.94)	0.77 (0.72-0.82)	NA	NA
- Model 2 [a]	4.54 (3.09-6.70)	0.78 (0.74-0.83)	0.71 (0.65-0.77)	8.5 (4.7-12.3)
- Model 3 [b]	2.95 (1.88-4.63)	0.83 (0.78-0.87)	0.80 (0.75-0.85)	2.8 (0.5-5.1)
Sample > 75 years				
All-cause mortality				
- Model 1	2.30 (1.75-3.01)	0.62 (0.58-0.67)	NA	NA
- Model 2 [a]	2.06 (1.57-2.69)	0.66 (0.61-0.70)	0.61 (0.56-0.65)	7.6 (3.8-1.4)
- Model 3 [b]	2.07 (1.49-2.86)	0.69 (0.65-0.74)	0.68 (0.64-0.72)	5.4 (1.8-9.0)
Cardiovascular mortality				
- Model 1	2.35 (1.54-3.58)	0.62 (0.55-0.69)	NA	NA
- Model 2 [a]	2.22 (1.45-3.40)	0.63 (0.56-0.70)	0.56 (0.48-0.63)	1.7 (0.0-3.4)
- Model 3 [b]	1.82 (1.08-3.05)	0.73 (0.67-0.78)	0.71 (0.65-0.77)	0.1 (0.0-0.7)

Table 2. Results of the Cox regression analyses of the logarithmically transformed MR-proANP, the comparison of predictive capability for mortality and cardiovascular events as determined by the Harrell's C statistic, and the IDI for adding the peptide to models 2 and 3, respectively. Abbreviations: HR, hazard ratio; CI, confidence interval; IDI, integrated discrimination improvement; NA, not applicable. [a] Adjusted for age and gender; [b] Adjusted for age, gender, smoking (dichotomous), body mass index, systolic blood pressure, duration of diabetes, serum creatinine level, cholesterol-HDL ratio, macrovascular complications (dichotomous), albuminuria (dichotomous), the use of lipid lowering and antihypertensive medications (dichotomous); * Harrell's C values for the models without MR-proANP.

Rates of cardiovascular mortality according to different levels of SBP and MR-proANP in patients older than 75 years are shown in figure 1. The number of cardiovascular deaths was the highest in patients with MR-proANP levels > median and SBP < median. The lowest number was observed in patients with MR-proANP levels < median and SBP > median. Hazard ratios (HRs) for all-cause and cardiovascular mortality according to different measures of blood pressure are shown in table 3. All blood pressure measures were inversely related to all-cause mortality. For cardiovascular mortality, we observed inverse relationships for SBP and PP. Adjustment for MR-proANP did not affect the relationship for any of the blood pressure measures.

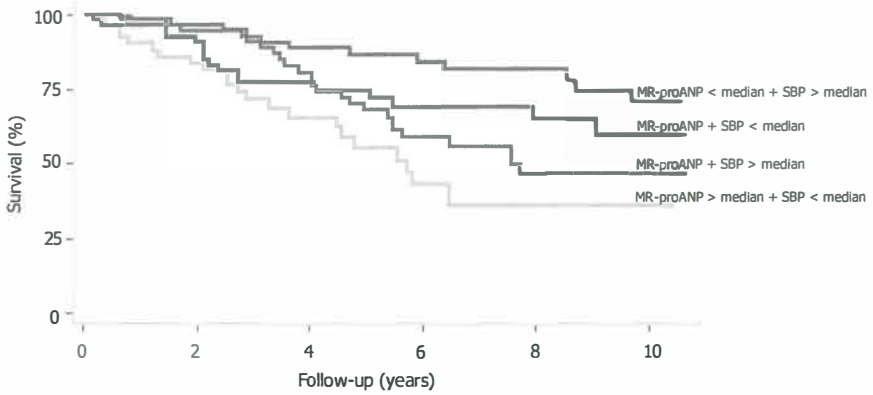

Figure 1. Kaplan-Meier curve; cardiovascular mortality. All elderly patients (n=225) were divided into 4 categories. From top to bottom the lines represent 1. MR-proANP < median and SBP > median, 2. MR-proANP and SBP < median, 3. MR-proANP and SBP > median, 4. MR-proANP > median and SBP < median.

Using updated mean blood pressure values and exclusion of deaths in the first two years of follow-up did not relevantly change the results (data not shown). The Groennesby and Borgan tests showed that all models were well calibrated.

	All-cause Mortality	Cardiovascular Mortality
Systolic blood pressure		
Multivariate	0.86 (0.80-0.93)	0.90 (0.79-1.00)
+ log MR-proANP	0.85 (0.78-0.92)	0.89 (0.78-0.99)
+ ANP 122 pmol	0.86 (0.79-0.93)	0.89 (0.79-1.00)
Diastolic blood pressure		
Multivariate	0.85 (0.73-0.99)	0.82 (0.64-1.03)
+ log MR-proANP	0.83 (0.71-0.96)	0.80 (0.64-1.01)
+ ANP 122 pmol	0.83 (0.71-0.97)	0.79 (0.62-1.04)
Pulse pressure		
Multivariate	0.85 (0.78-0.93)	0.90 (0.78-1.04)
+ log MR-proANP	0.84 (0.76-0.92)	0.90 (0.78-1.04)
+ ANP 122 pmol	0.85 (0.77-0.93)	0.90 (0.78-1.04)

Table 3. Hazard ratios of blood pressure indices for all-cause and cardiovascular mortality in patients >75 years. The hazard ratios (95% confidence interval) refer to a pressure increase of 10 mm Hg. In the multivariate model gender, smoking (yes or no), body mass index, duration of diabetes, serum creatinine level, cholesterol-HDL ratio, macrovascular complications (yes or no), albuminuria (yes or no), the use of lipid lowering and antihypertensive medications (yes or no), and age were selected as potential confounders. In the other models we additionally adjusted for either Log MR-proANP as a continuous variable, or MR-proANP with 122 pmol/L as a cut-off value.

Discussion

Three main conclusions can be drawn from this study. Firstly, higher serum levels of MR-proANP were associated with increased all-cause and cardiovascular mortality in patients with type 2 diabetes, irrespective of age. Secondly, the consistently lower Harrell's C values in old age showed that the predictive capabilities of MR-proANP diminish with advancing age. Thirdly, the inverse relationship between blood pressure and mortality in old age was not affected by additional adjustment for baseline serum levels of MR-proANP, used as a surrogate marker of heart failure.

Adding MR-proANP to models with age, gender and other cardiovascular risk factors resulted in increased predictive capabilities, as measured with the Harrell's C and IDI statistics, of both all-cause and cardiovascular mortality. Although MR-proANP has prognostic value for cardiovascular events in patients from the general population, results from previous studies showed conflicting results concerning the association with cardiovascular mortality [5,9,10]. In a recently published study in the general population, significant associations were only found for all-cause mortality [9]. However, based on the width of the 95% confidence interval, a relevant association between MR-proANP and cardiovascular mortality could not be excluded. In a study with chronic heart failure patients, the relationship between MR-proANP and cardiovascular mortality was similar to the one with all-cause mortality [10].

The predictive capabilities of the various models, as measured with the Harrell's C statistics, increased by adding more variables to the models. Adding MR-proANP to the models with all conventional risk factors, resulted in small increases in the C values. The lowest C values were observed in the group of elderly patients, indicating that the prognostic properties of MR-proANP diminish with advancing age. The IDI for adding MR-proANP to the fully adjusted models in the sample ≤ 75 years was significant for both all-cause and cardiovascular mortality. For elderly patients, improvements in the IDI were only observed for the models investigating all-cause mortality. A plausible explanation for the diminishing properties with advancing age may be the phenomenon of competing risks: the effect of a certain risk factor on mortality declines with advancing age since other risk factors, including age itself, become more important with advancing age [24].

In the present study we had no data on NT-proBNP and therefore we were not able to perform a head-to-head comparison. Previous studies, however, have shown that MR-proANP has comparable prognostic and diagnostic capabilities as NT-proBNP, and can be considered as an alternative for NT-proBNP [6-9]. Although our study showed that MR-proANP is an independent risk factor for mortality, its practical implications still remain to be determined. Based on the

small improvements in Harrell's C values when adding biomarkers to the adjusted models, one may conclude that the additional value of MR-proANP in risk prediction seems rather limited. However, it is important to realise that it is difficult to achieve further improvements in risk prediction by adding a biomarker to models with all conventional risk factors [5]. In the present study, the C values of the fully adjusted models without MR-proANP in the overall population were 0.79 and 0.80 for all-cause and cardiovascular mortality, respectively. These values leave little room for further improvements in risk prediction.

To our knowledge, this is the first study investigating whether adjustment for natriuretic peptides influences the inverse relationship between blood pressure and mortality in old age. It is important to emphasize that, due to the observational design of our study, no conclusions about causality can be drawn. The results from figure 1, in which the highest mortality rate was observed in patients with the highest MR-proANP levels and the lowest SBP levels, suggest that heart failure may explain the inverse relationship. However, these results were not confirmed by the Cox regression analyses. Even though we tried to adjust for co-morbidities and frailty in our analyses, it is not unlikely that these factors still account for the inverse relationship (residual confounding). Odden et al. showed that the relationship between mortality and blood pressure is influenced by walking speed, which can be regarded as a marker of frailty. Higher blood pressure was only associated with increased mortality among faster walkers, and no relationship was found for slow walkers [25]. A subgroup analysis of the ADVANCE trial, in which predominantly healthy elderly patients were included, showed beneficial results of antihypertensive treatment in patients with type 2 diabetes aged older than 75 years [26]. These results confirm the hypothesis that blood pressure is especially an important target for treatment in healthy elderly patients with a low level of frailty. Side-effects of antihypertensive medication and excessive lowering of blood pressure should also be considered as explanations for the inverse relationships observed. For example, in the International Verapamil SR-trandolapril trial, a study amongst patients with type 2 diabetes and coronary artery disease, a systolic blood pressure below 115 mmHg was associated with increased mortality [27]. Since the majority of our elderly population had hypertension (84%) and approximately 64% received antihypertensive treatment, confounding by indication may also have led to the inverse relationships.

The main limitation of our study is its observational design. Also, the results of our blood pressure analyses should be used as hypothesis-generating only, since the use of baseline serum MR-proANP levels as a surrogate measure of heart failure has several limitations. Firstly, because we only adjusted for a single baseline MR-proANP value we were not able to adjust for heart failure that has developed during the follow-up period, as well as for potential variability in concentrations. Secondly, the evidence for which cut-off values should be used in the

diagnosis of chronic heart failure is limited. The cut-off value we used was established in a study which compared the prognostic properties of MR-proANP and NT-proBNP [10]. Thirdly, levels of natriuretic peptides tend to increase with higher age which makes it more problematic to use these peptides as a marker of heart failure. On the other hand, we did observe increased mortality with higher levels of MR-proANP. Another limitation is that ranges of meaningful improvements are not established for the IDI [22]. Furthermore, the IDI has originally not been developed for censored data as ours. Therefore, the results are difficult to interpret and caution is needed when basing conclusions on the IDI. Strengths of our study were its prospective design, the high number of deaths after the 10-year follow-up period and the additional analyses, including the updated mean method, we performed.

We conclude that this study showed that MR-proANP is independently associated with all-cause and cardiovascular mortality in patients with type 2 diabetes, and that its predictive capabilities decreased with advancing age.

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Chapter 6

Chronic kidney disease and mortality risk among older patients with type 2 diabetes mellitus (ZODIAC-24)

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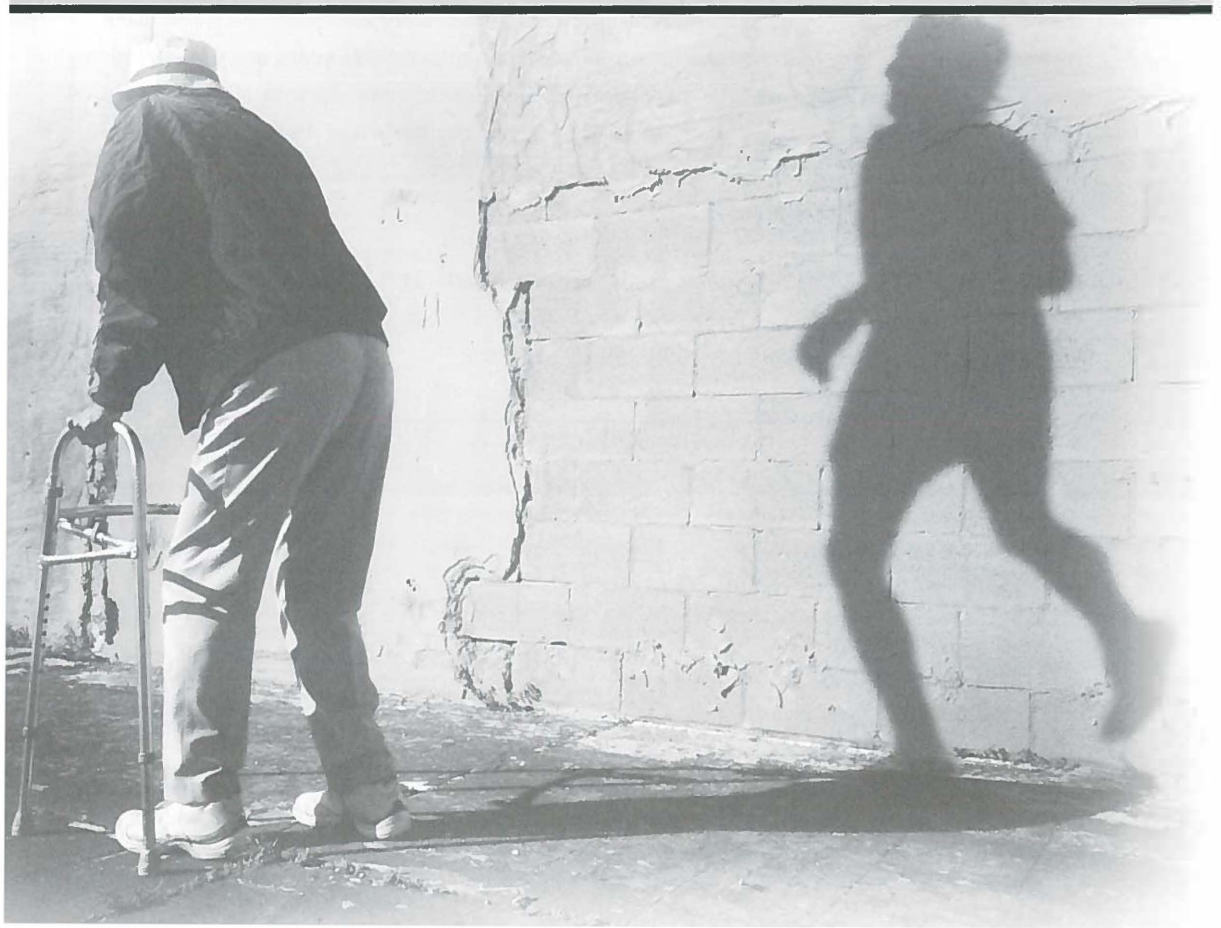

Abstract

Objective: To investigate the association between a decreased estimated glomerular filtration rate (eGFR), albuminuria and mortality in elderly patients with type 2 diabetes mellitus (T2DM).

Design: Prospective observational cohort study.

Setting: Primary care.

Subjects: 810 patients, ≥65 years with T2DM. Analyses were performed in age strata: 65-75 (n=471), >75 (n=339) years.

Methods: Cox proportional hazard modeling was used to investigate the association between eGFR, albuminuria and all-cause and cardiovascular mortality after a median follow-up of 9.8 years.

Results: An eGFR <45 and 45-60ml/min/1.73m² was associated with increased cardiovascular mortality in patients of 65-75 years, hazard ratio (HR): 3.29 (1.58-6.86) and 1.78 (1.09-2.90), respectively; in those >75 years increased cardiovascular mortality was observed when eGFR was <45ml/min/1.73m²: 2.42 (1.47-3.69). Compared to patients of 65-75 years, an eGFR >60ml/min/1.73m² and normo-albuminuria, fully adjusted HRs for cardiovascular mortality were 2.26 (1.04-4.92) and 4.86 (2.33-10.15) for those aged 65-75 years, an eGFR of 45-60ml/min/1.73m² and normo-albuminuria or albuminuria, respectively; HRs were 1.33 (0.67-2.66) and 2.01 (1.02-3.94), respectively for those >75 years.

Conclusions: An eGFR of 45-60ml/min/1.73m² in T2DM patients is associated with increased mortality in patients aged 65-75 years but not in those >75 years. Albuminuria is associated with increased mortality in patients >65 years.

Introduction

Chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease (CVD), cardiovascular mortality as well as all-cause mortality [1-3]. As a consequence, there has been increasing focus on the prevention and early detection of CKD. Some of the present CKD guidelines recommend follow-up and treatment when the estimated glomerular filtration rate (eGFR) falls below 60 ml/min/1.73m^2 [4]. However, a substantial part of the older population has an eGFR <60 ml/min/1.73m^2. The clinical significance of moderate reductions of eGFR in older people is still debated [5-7]. Some argue that in the absence of other abnormalities, an age-related decrease in eGFR is physiological; others state that reduction of eGFR in individuals >65 years may reflect the high prevalence of kidney disease risk factors at older age [8]. In spite of the uncertainties regarding clinical significance, follow-up of renal function is indicated, since older patients can also have an underlying renal disease or factors adding to the progression of kidney disease.

The number of older people with type 2 diabetes mellitus (T2DM) is increasing thanks to earlier diagnosis and better survival. Therefore complications, such as diabetic nephropathy occur more frequently [9] and screening for kidney disease has become a cornerstone of diabetes care [10]. However, the association between eGFR, albuminuria and mortality has been sparsely investigated in older diabetic patients [11]. Moreover, classic cardiovascular risk factors seem to have a diminished effect when assessed in patients >75 years [12-13]. Therefore, we aimed to investigate the association between eGFR , albuminuria and mortality in older patients with T2DM, stratified according to age (65-75 years and >75 years).

Methods

In 1998, the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) study was initiated in the Zwolle region, the Netherlands. The design and details of this study have been presented elsewhere [14]. Briefly, the ZODIAC study is part of a shared care project, in which general practitioners are assisted by hospital-based nurses specialised in their care of patients with T2DM. At baseline, patients being treated by a specialist of internal medicine (20%) or patients with a very short life expectancy (including patients with active cancer) or insufficient cognitive abilities as judged by the general practitioner, were excluded. Ultimately, general practitioners excluded 5% of the patients treated in primary care forT2DM.

Approximately 90% (n=1357) agreed to participate; four patients were excluded because of insufficient baseline data. For the present study we selected all patients ≥65 years with complete information on all confounders (n=810). The ZODIAC study was approved by the medical ethics committee, and all patients provided informed consent.

Data collection

Baseline data were collected from 1998-1999 and consisted of a full medical history including assessment of macrovascular complications, medication use, diabetes duration and tobacco consumption. Macrovascular complications were defined as a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke or transient ischaemic attack. Laboratory and physical assessment data were collected annually and included glycated haemoglobin (HbA_{1c}), non-fasting lipid profile, plasma creatinine (a kinetic colorimetric Jaffé method was used (Modular P Analyzer, Roche Almere, the Netherlands)), albumin-to-creatinine ratio (ACR, assessed in a spot morning urine sample using immunonephelometry (Behring Nephelometer; Mannheim, Germany)), blood pressure (measured twice with a Welch Allyn sphygmomanometer), bodyweight and height. Renal function was estimated by the Modification of Diet in Renal Disease equation (MDRD) [15]. MDRD was categorized into 3 classes: <45, 45-60 and ≥60 ml/min/1.73m². Albuminuria was defined as an ACR ≥2.5 mg/mmol in men and ≥3.5 mg/mmol in women. The overall cohort (n=810) was divided into a low (65-75 years, n=471) and a high age group (>75 years, n=339).

Clinical endpoints

Two clinical endpoints were examined: all-cause and cardiovascular mortality. In 2009, the vital status and cause of death were retrieved from records maintained by the hospital and general practitioners.

Statistical analyses

SPSS version 16.0 (SAS Insitute, Cary, NC, USA) and STATA version 11.0 (Stata Corp., College Station, TX, USA) were used for statistical analyses. A Cox proportional hazard model was used to investigate the association between eGFR, ACR and mortality with adjustment for selected confounders. The associations were investigated for the eGFR as a categorical variable as well as a continuous variable (using baseline MDRD values) and for albuminuria as a categorical variable. Hazard ratios (HRs) for covariates were calculated for changes in eGFR of 10 ml/min/1.73m². The following possible confounders were selected: age, gender, smoking (dichotomous), body mass index, systolic blood pressure, history of macrovascular complications (dichotomous), diabetes duration, HbA_{1c}, use of carbasalate calcium, use of lipid lowering medications, the total cholesterol-HDL ratio and albuminuria (dichotomous), the eGFR was added and albuminuria was removed as a confounder when the association between (normo)albuminuria and mortality was tested.

Three different models were analyzed: model 1 (crude), model 2 (including all selected confounders) and model 3 in which all selected confounders were used, except variables that were already used in the MDRD (sex and age). The latter model was performed to reduce the

phenomenon of multicollinearity and to evaluate the influence of omitting these variables on the association between renal function predicted by the MDRD, and mortality. Cox regression analyses were performed to investigate the association of albuminuria with all-cause and cardiovascular mortality; these analyses were repeated in eGFR categories ≤ and >60 ml/min/1.73m² with and without albuminuria. Since stratification by the level of ACR may be warranted in terms of association with mortality, we tested the interaction between the MDRD (as continuous and as categorical variable) and the ACR. For Kaplan-Meier curves eGFR baseline values were categorised into three different groups: <45, 45-60 and >60 ml/min/1.73m².

Results

Baseline characteristics of the population are shown in table 1. Patients >75 years had an eGFR <60 ml/min/1.73m² (n=213; 63%) and albuminuria (n=176; 52%) more frequently than patients aged 65-75 years (n=195, 41% and n=209, 44%, respectively). 274 patients (81%) in the high age group and 170 patients (36%) in the low age group died after a follow-up time of 10 years. In 27 patients (3%) the cause of death was unknown, 19 patients were lost to follow-up. The proportion of deaths attributable to cardiovascular causes was 43% in the high age group and 42% in the low age group.

	65-75 years *n=471*	**>75 years** *n=339*
Age (years)	71 [68, 73]	79 [77, 83]
Men	192 (41%)	122 (36%)
Body mass index (kg/m²)	29 (5)	27 (4)
Systolic blood pressure (mmHg)	159 (24)	156 (25)
Diastolic blood pressure (mmHg)	84 (11)	81 (11)
Current smoking	66 (14%)	32 (9%)
Cholesterol-HDL ratio	5.2 (1.5)	4.9 (1.6)
HbA_{1c} (mmol/mol)	58	57
Macrovascular complications present	175 (37%)	150 (44%)
Receiving antihypertensive treatment	263 (53%)	234 (62%)
Receiving carbasalate calcium	65 (14%)	61 (18%)
Receiving lipid lowering treatment	61 (13%)	15 (4%)
Duration of diabetes mellitus type 2 (years)	6 [3, 12]	8 [4, 13]
Plasma creatinine (µmol/l)	92 [82, 105]	98 [85, 115]
MDRD (ml/min/1.73m²)	63 [55, 71]	56 [48, 66]
<45	6%	21%
45-60	35%	42%
>60	59%	37%
Albuminuria present	209 (44%)	176 (52%)

Table 1. Baseline characteristics. Data are means (±SD), medians (interquartile range) or *n* (%).

Renal function estimates and plasma creatinine

Tables 2 and 3 present the hazard ratios (HRs) for cardiovascular and all-cause mortality for eGFR categories and (normo)albuminuria. The MDRD as a continuous variable was associated with both increased all-cause as well as cardiovascular mortality in all models of both age groups. After adjusting for confounders, the cardiovascular mortality risk increased by 64% [95% confidence interval (95% CI): 33-96%] and 47% [95% CI: 25-75%] for every 10 ml/min/1.73m^2 decrease in eGFR in the low and high age group, respectively (model 3).

Patients with an eGFR <45 ml/min/1.73m^2 in the high age group, had an increased risk for all-cause and cardiovascular mortality compared to the reference category (>60 ml/min/1.73m^2). Such a relationship was not observed for eGFR values between 45 en 60 ml/min/1.73m^2. In contrast in patients aged 65-75 years, cardiovascular mortality risk was increased in patients with eGFR values between 45-60 ml/min/1.73m^2. The HRs of model 1 and 2 for all-cause mortality in this age group were not significant for patients with an eGFR <60 ml/min/1.73m^2. However, the results of model 3 show that the risk of all-cause mortality was increased for patients with an eGFR value below 60 ml/min/1.73m^2 compared to higher levels. Figure 1 shows the association between eGFR and mortality in both the low and the high age group.

Albuminuria

In both age groups, albuminuria was associated with all-cause and cardiovascular mortality (tables 2 and 3). Compared to participants aged 65-75 years with an eGFR >60 ml/min/1.73m^2 and normo-albuminuria, the fully adjusted HRs for cardiovascular mortality were 2.26 (95% CI 1.04-4.92) for impaired eGFR (45-60 ml/min/1.73m^2) and normo-albuminuria, and 4.86 (95% CI 2.33-10.15) for those with an eGFR of 45-60 ml/min/1.73m^2 and albuminuria. For participants aged >75 years, HRs were 1.33 (0.67-2.66) and 2.01 (1.02-3.94), respectively.

No interaction between the MDRD and ACR was present for both age groups (MDRD categorical: p-value 0.085 and 0.575; MDRD continuous p-value 0.767 and 0.386 for patients aged 65-75 and >75 years, respectively).

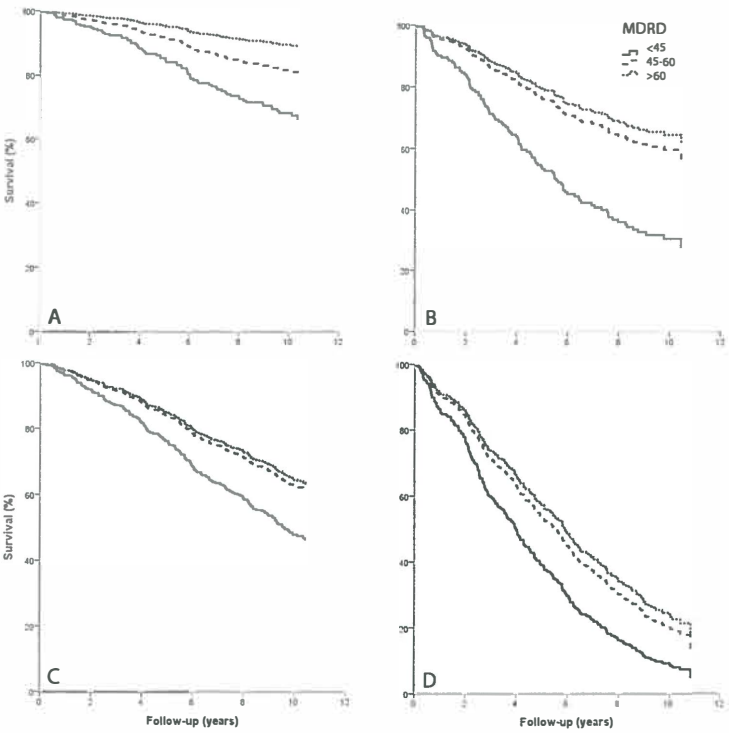

Figure 1. Kaplan Meier curves showing the association between estimated glomerular filtration rate and mortality. Panels A and B show the curves for cardiovascular mortality for patients aged 65-75 years (A) and for patients aged >75 years (B). Panels C and D show the curves for all-cause mortality for patients aged 65-75 years (C) and for patients aged >75 years (D).

		Cardiovascular mortality					
		65-75 years			>75 years		
		*Model 1	#Model 2	$Model 3	*Model 1	#Model 2	$Model 3
Estimated glomerular filtration rate	Continuous Per 10 ml/min/1.73m² decrease	1.61 (1.35-1.96)	1.69 (1.37-2.08)	1.64 (1.33-1.96)	1.43 (1.22-1.67)	1.45 (1.20-1.69)	1.47 (1.25-1.75)
	>60 ml/min/1.73m²	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	45-60 ml/min/1.73m²	1.95 (1.20-3.16)	1.87 (1.08-3.23)	1.78 (1.09-2.90)	1.15 (0.73-1.79)	1.08 (0.67-1.73)	1.15 (0.73-1.81)
	<45 ml/min/1.73m²	3.57 (1.75-7.29)	3.65 (1.65-8.07)	3.29 (1.58-6.86)	2.56 (1.59-4.12)	2.51 (1.51-4.19)	2.42 (1.47-3.96)
Albumin-to-creatinine ratio	normoalbuminuria	1.00 (ref)	1.00 (ref)	NA	1.00 (ref)	1.00 (ref)	NA
	albuminuria	2.60 (1.63-4.15)	1.94 (1.18-3.21)	NA	1.59 (1.09-2.32)	1.49 (0.99-2.24)	NA

Table 2. Hazard ratios for eGFR and cardiovascular mortality. * Model 1 is unadjusted. # Model 2 is adjusted for: age, gender, smoking (dichotomous), body mass index (BMI), systolic blood pressure, a history of macrovascular complications (dichotomous), diabetes duration, HbA_{1c}, albuminuria (dichotomous), the total cholesterol-HDL ratio, the use of carbasalate calcium and lipid lowering treatment; $ Model 3 is adjusted for the same variables as in model 2 except for those who are already used for calculation of the MDRD (age, sex). In model 2 ACR no correction takes place for albuminuria (dichotomous); in model 2 ACR, correction for eGFR does occur. NA: not applicable.

		All-cause mortality					
			65-75 years			>75 years	
		*Model 1	#Model 2	$Model 3	*Model 1	#Model 2	$Model 3
Estimated glomerular filtration rate	Continuous Per 10 ml/min/1.73m² decrease	1.16 (1.03-1.32)	1.22 (1.06-1.41)	1.19 (1.05-1.35)	1.12 (1.03-1.25)	1.12 (1.02-1.27)	1.16 (1.05-1.28)
	>60 ml/min/1.73m²	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	45-60 ml/min/1.73m²	1.10 (0.81-1.50)	1.11 (0.79-1.57)	1.82 (1.10-2.99)	0.99 (0.75-1.31)	1.03 (0.76-1.38)	1.18 (0.74-1.87)
	<45 ml/min/1.73m²	1.48 (0.85-2.59)	1.72 (0.94-3.14)	3.57 (1.69-7.54)	1.63 (1.18-2.25)	1.63 (1.15-2.30)	2.69 (1.63-4.43)
Albumin-to-creatinine ratio	normoalbuminuria	1.00 (ref)	1.00 (ref)	NA	1.00 (ref)	1.00 (ref)	NA
	albuminuria	2.04 (1.52-2.73)	1.52 (1.11-2.07)	NA	1.45 (1.14-1.85)	1.60 (1.23-2.08)	NA

Table 3. Hazard ratios for eGFR and all-cause mortality. * Model 1 is unadjusted. # Model 2 is adjusted for: age, gender, smoking (dichotomous), body mass index (BMI), systolic blood pressure, a history of macrovascular complications (dichotomous), diabetes duration, HbA_{1c}, albuminuria (dichotomous), the total cholesterol-HDL ratio, the use of carbasalate calcium and lipid lowering treatment; $ Model 3 is adjusted for the same variables as in model 2 except for those who are already used for calculation of the MDRD (age, sex). In model 2 ACR no correction takes place for albuminuria (dichotomous); in model 2 ACR, correction for eGFR does occur. NA: not applicable.

Discussion

In this study renal function loss was related to both increased all-cause and cardiovascular mortality. In patients >75 years, increased all-cause and cardiovascular mortality was only observed when the eGFR was <45 ml/min/1.73m², this in contrast to elderly patients aged 65-75 years in which an increased risk for cardiovascular mortality was observed when renal function estimates dropped below 60 ml/min/1.73m². Albuminuria was independently associated with all-cause and cardiovascular mortality irrespective of eGFR in both age groups. The fact that in model 3 the risk of all-cause mortality was increased for patients with an eGFR value <60 ml/min/1.73m² compared to higher levels, shows that multicollinearity occurs when age and sex are, next to its presence in the MDRD formula, also used as a confounder (such as in model 2).

Thus, age seems to be an important effect modifier in CKD. A meta-analysis in general population cohorts showed independent and joint associations of albuminuria and eGFR <60 ml/min/1.73m² on cardiovascular and all-cause mortality [16]. However, the number of patients >70 years was relatively small and associations were not evaluated in separate age cohorts. Other studies investigating the consequences of a reduced eGFR in patients >75 years in the general population have shown that if normoalbuminuric, mortality risk is only increased when eGFR is <45 ml/min/1.73m² [17-19]. Moreover, older patients had higher rates of death and lower rates of end-stage renal disease than younger patients at comparable levels of eGFR [20]. From a cross-sectional study in older people, it appeared that an eGFR <45 ml/min/1.73m² mainly identifies a smaller subgroup of people >75 years with significant comorbidity, impaired functional state and a high risk of potentially reversible consequences (e.g. anaemia) [21].

Most of the above mentioned studies contained only few diabetes patients or patients >75 years. A study among diabetic patients >65 years showed that albuminuria and an eGFR <60 ml/min/1.73m² were independent risk factors for mortality [2]. However, the observed relationship might have been largely attributable to the proportion of patients with an eGFR <45 ml/min/1.73m². Our results show that even in normo-albuminuric patients with T2DM, >75 years, an eGFR of 45-60 ml/min/1.73m² is not associated with an increased risk for cardiovascular and all-cause mortality, in contrast to those aged 65-75 years. Our results are confirmed by a recent meta-analysis in normo-albuminuric patients at high risk for CKD (n=106690, 40% had diabetes), whose risk for all-cause mortality was increased at eGFR levels <60 ml/min/1.73m² [3]. However, in subjects ≥65 years, significance was reached at a lower level (<45 ml/min/1.73m²), as opposed to subjects <65 years. No specific analyses were made for patients>75 years.

The attenuation of the association of mortality with certain eGFR stages in older patients as we observed, was not found for albuminuria. This is confirmatory with previous studies. An independent association between proteinuria and mortality has been shown in patients with and without diabetes. In the HUNT II study, the presence of micro-albuminuria or high-normal ACR ratios was associated with increased cardiovascular mortality below the threshold of 75 ml/min/1.73m^2 compared to those with normo-albuminuria [18]. A more recent study found in a largely male cohort that the ACR in diabetes patients >65 years was independently associated with mortality at all levels of eGFR [11]; an observation that is in agreement with our study. In contrast to our study, a large study in primary care, investigating the association between dipstick proteinuria, eGFR and mortality in patients aged >75 years, the presence of dipstick proteinuria did not add to cardiovascular mortality risk. This is remarkable since one would expect that especially when a dipstick is used, the risk of cardiovascular mortality would have been higher [19]. Also another study in older individuals referring patients with CKD stage 4 did not find a statistically significant association between level of proteinuria and risk of death; 33% was >75 years) [23]. An explanation for the discrepancy in the two last mentioned studies and our study results has not been found.

The absence of an association of moderate reduction in eGFR with mortality at older age may have been caused by the fact that the MDRD was not developed for use in older patients. Moreover, creatinine is a poor marker of renal function in these patients leading to inaccuracy [24-25]. Secondly, older patients have higher background mortality and a higher prevalence of comorbidity [26]. Finally moderate reductions in eGFR may reflect a physiological decline in renal function with advancing age [27-28]. Since albuminuria reflects another pathway of kidney damage than eGFR, this may explain we found no attenuation of the association between albuminuria and increased cardiovascular mortality [29-30].

Our study has some methodological aspects that need discussion. Firstly, our study cohort is rather small, especially the group with an eGFR <45 ml/min/1.73m^2. Therefore the results should be interpreted with caution. Due to the small numbers no differentiation in micro- and macroalbuminuria was made since the number of patients in the separate groups would become too small. Secondly, we have used uncalibrated plasma creatinine measurements. This might have induced systematic errors in eGFR values. Fortunately, all creatinine measurements were performed in the same laboratory, so interlaboratory variation was excluded. Selection bias may have occurred, since patients with a short life expectancy and patients treated in hospital for their diabetes were excluded. Finally, the MDRD has not been validated in patients >70 years. Strengths are the prospective nature, the possibility to take into account many possible confounders with few missing data, and the long follow-up.

In conclusion, patients >75 years with T2DM and an eGFR of 45-60 ml/min/1.73m^2 are not at increased risk for all-cause and cardiovascular mortality compared to their counterparts with an eGFR >60 ml/min/1.73m^2. In contrast albuminuria at all levels of eGFR is strongly associated with increased all-cause and cardiovascular mortality, and therefore may have potential as a more discriminative risk stratification tool in the large group of older patients with moderate reductions in eGFR (45-60 ml/min/1.73m^2). In this study, as in most studies of CKD in older individuals, patients with moderate decrements of renal function account for a large proportion of the older population with CKD, which suggests that the current staging system, taking into account eGFR only, may not be a reliable tool for older patients, at least when used to assess increased cardiovascular risk.

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Chapter 7

Health related quality of life and mortality in a general and elderly population of patients with type 2 diabetes (ZODIAC-18)

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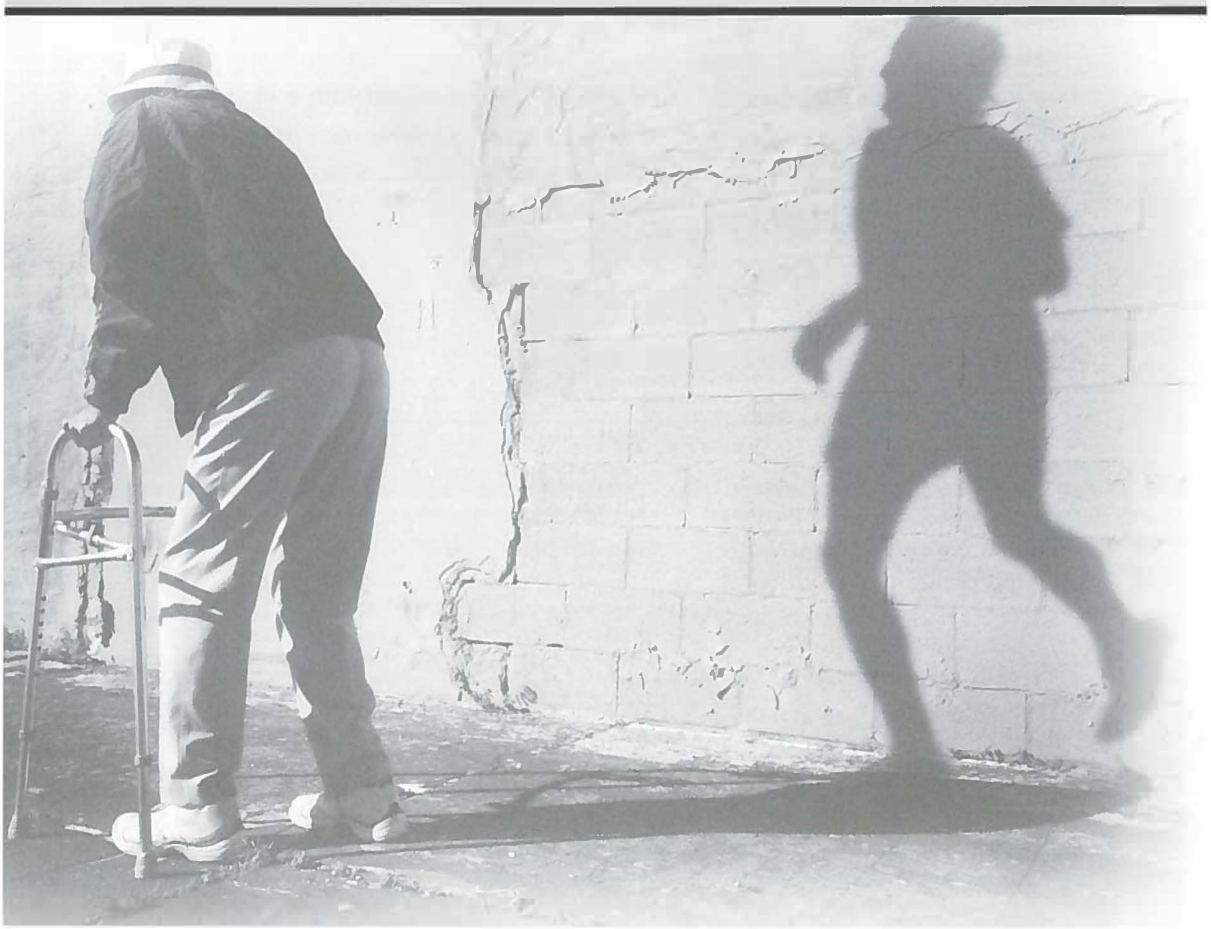

Abstract

Objective: Diabetes negatively impacts the health related quality of life (HRQOL) of patients with type 2 diabetes mellitus (T2DM). An earlier analysis showed HRQOL to be associated with mortality, which suggests that measuring HRQOL could have clinical implications. We studied the association between HRQOL and total and cardiovascular mortality in patients with T2DM during long term follow-up and specifically focused on old age and gender differences.

Research design and methods: HRQOL was measured in a prospectively followed cohort of 1353 patients with T2DM using the RAND-36. Cox proportional hazard models were used to measure the independent effect of baseline HRQOL on mortality.

Results: During a mean follow-up of 9.6 years, 570 (42%) patients died, 238 of whom died of cardiovascular disease (42%). The Physical Component Score (PCS) and the Mental Component Score (MCS) were inversely associated with total mortality, with HRs of 0.988 (95%CI 0.983-0.993) and 0.990 (95%CI 0.985-0.995), respectively. A 10 point higher score, on the PCS and MCS decreased the risk for total mortality with 11% and 10%, respectively. An inverse relationship with mortality was also seen for men, women, and for patients aged >75 years. Mental health was significantly related to mortality in men but not in women.

Conclusions: Lower physical and mental HRQOL was associated with a higher total and cardiovascular mortality in patients with T2DM, also when studying men and women, as well as elderly separately. The dimension mental health, related to depression and anxiety, was only associated with mortality in men, not in women.

Introduction

Diabetes often leads to the development of physical disabilities which, in turn can have a detrimental effect on a patient's quality of life (1). The importance of optimizing HRQOL has increasingly been recognized. Not only because it represents an important goal for health care in its own, but also because of the associations between poor HRQOL and adverse outcomes in people with type 2 diabetes mellitus (T2DM), including poor response to therapy, disease progression and even mortality [2-6].

The relationship between HRQOL and mortality in patients with diabetes has been investigated previously in three studies (4-6). López Revuelta et al. (4) showed 'perceived mental health' to be an independent predictor of morbidity and mortality in patients with end-stage renal disease. Most of the patients in this study had diabetes (65%). In a recently published study, the EQ-5D questionnaire was used to study the relationship between HRQOL and mortality, and lower HRQOL was associated with a higher mortality rate (5). Our study group previously showed the 'physical component summary' of the RAND-36 to be an independent marker for total mortality in patients with T2DM (6). The investigators in two of the three aforementioned studies reported results for individual health dimensions (4,6). 'Physical functioning' and 'general health' in Kleefstra et al.'s study (6) and 'general health', 'mental health', and 'role limitations due to emotional problems' in López Revuelta et al.'s study (4) were associated with total mortality. Although previous studies have shown an inverse relationship between HRQOL and mortality in the elderly population (7-9), no study has specifically focused on the elderly patients with T2DM. Traditional risk factors become less predictive of mortality at increasing age (10). HRQOL is therefore of interest for elderly patients, and may become increasingly important to clinicians for its predictive value.

After these three studies, questions still remain on the relationship between the different health dimensions and mortality, the relationship between HRQOL and mortality in elderly patients with T2DM and whether the relationship between HRQOL and mortality is different between men and women. The purpose of this study was to revisit the association between HRQOL and mortality after a longer follow-up period (10 years) with a special focus on the elderly (>75 years) and on possible gender differences.

Patients and Methods

In 1998, in the Zwolle region of the Netherlands, a large diabetes project was initiated. In the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC), general practitioners (GPs) were assisted by hospital based diabetes specialist nurses in providing care for patients

with T2DM. As part of this project, patients with T2DM in 32 primary care practices consulted (and still consult) these specialist nurses on an annual basis. Patients with a very short life expectancy (including patients with active cancer) and patients with insufficient cognitive abilities were excluded from the study. All patients with T2DM were identified during the first two years of the project. Any patients being treated by a specialist of internal medicine (20%) were excluded as they were no longer in the primary care setting. Five percent of patients were excluded because of a short life expectancy or because they had insufficient cognitive abilities to complete the necessary questionnaires. 1353 (90%) patients agreed to participate in the study. The ZODIAC Study was approved by the medical ethics committee, and all patients provided informed consent. The details of this study have been published previously (11).

Baseline data, collected in 1998 and 1999, included the RAND-36 Questionnaires, a full medical history including the presence or absence of macrovascular complications, the use of medication, and tobacco consumption. Laboratory and physical assessment data were collected annually, and included a lipid profile, HbA1c, serum creatinine, urinary albumin, urinary creatinine, blood pressure, weight, and height. Subsequently, life status and causes of death were retrieved from the records maintained by the hospital and the GPs. The causes of death were coded according to The International Classification of Diseases, 9th Revision (ICD-9).

The RAND-36 is considered a generic measure as it is used to assess aspects of health which are relevant to any individual's functional status and well being (12,13). The RAND-36 consists of 36 questions covering 9 aspects of health status: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, mental health, and health change. The scores for questions relating to each scale are summed and rescaled to a 100-point scale, where 100 is the best possible score and 0 the worst. The nine scales in the RAND-36 can further be divided into two component summaries: a Physical Component Summary (PCS) and a Mental Component Summary (MCS) (12,14). Low PCS scores indicate substantial limitations in self-care, physical and social activities, severe bodily pain, or frequent tiredness. Low MCS scores indicate frequent psychological distress, and substantial social and role limitations due to emotional problems.

To study mortality, standardized mortality ratios (SMR) were calculated for total and cardiovascular mortality using general mortality reference rates from the Netherlands (Available from http://statline.cbs.nl/StatWeb/). Cox proportional hazard modelling was used to assess the association between HRQOL and total as well as cardiovascular mortality. The health dimensions and component scales all have a different mean value between countries. Comparing scales between countries is therefore difficult. We therefore transformed the

scales. The transformation used is a linear T-score transformation with reference data from the Netherlands (15), which has the advantage of making the different dimensions of health easier to interpret without further reference to normative data (14,16). This results in scores for all the dimensions and the summary scores to have a mean of 50 and a standard deviation of 10. The use of the same mean and standard deviation for purposes of transforming scores has the advantage of permitting comparisons of mean scores for HRQOL across countries (17).

A model was constructed which included all possible confounders in the analysis (see below). Separate analyses were performed to study the effect of age and gender on mortality. For the age specific analysis, patients were stratified into two age groups, those aged older than 75 years, and those aged 75 years and younger. For the gender specific analysis we investigated, whether significant interaction takes place between gender and HRQOL. Subsequently, we performed multivariate analyses stratified according to gender. The following variables as possible confounders were included: age, gender, smoking (yes/no), duration of diabetes, serum creatinine, body mass index, systolic blood pressure, total cholesterol to HDL-cholesterol ratio, macrovascular complications (yes or no), use of statins (yes or no), insulin use (yes or no), and urinary albumin-creatinine ratio. The proportional hazards assumption was examined using log (-log) survival plots. The parallel lines in the plots indicate that the assumption was met. All tests were 2-sided and analyses were performed with SPSS version 15.0.1 (SPSS inc., Chicago, Illinois, USA).

Results

Patient characteristics at baseline are presented in table 1. After a median follow-up period of 9.6 years, 570 of the 1353 patients had died (42%). Life status was not known for 20 patients (1%), and causes of death were unknown for 29 patients (5%); 238 deaths (42%) had cardiovascular causes, and 122 deaths (21%) were due to cancer. HRQOL data were available and complete for 1053 patients (78%). The SMRs (95% confidence interval (95%CI)) for total mortality and cardiovascular mortality were 2.35 (95%CI 1.77-3.04) and 2.67 (95%CI 2.36-3.05).

	Total *n=1353*	Deceased patients *n=570*	Survived patients *n=783*
Age (years)	67.8 (±11.7)	75.3 (±8.6)	62.4 (±10.6)‡
Female (%)	57.6	57.2	57.9
Diabetes duration (years)	6 (3-11)	7 (3-13)	5 (2-10)‡
Smoking (%)	18.6	14.8	21.4
BMI (kg/m^2)	28.9 (±4.8)	28.3 (±4.7)	29.4 (±4.7)‡
Systolic blood pressure (mm Hg)	153 (±25)	156 (±27)	152 (±24)*
HbA1c (%)	7.5 (±1.2)	7.4 (±1.3)	7.5 (±1.2)
Creatinine clearance (ml/min)	73.9 (±28.1)	60.3 (±22.2)	83.8 (±27.9)‡
Total cholesterol-HDL ratio	5.2 (±1.6)	5.1 (±1.6)	5.2 (±1.5)
Albumin-creatinine ratio	2.1 (1.0-7.2)	3.9 (1.4-12.3)	1.6 (0.9-4.4‡
Macrovascular complications (%)	32.7	46.1	23.0‡
Age >75 years (%)	27.6	53.3	8.9‡
PCS score	71.6 (48.7-86.7)	61.3 (41.5-80.5)	76.8 (55.8-89.2)‡
MCS score	76.8 (59.3-87.6)	71.3 (52.3-84.1)	79.8 (61.8-88.8)‡

Table 1. Baseline characteristics. Data are presented as mean ±SD for normally distributed data and as median with interquartile range for non-normally distributed data or %, * P<0.05, † P<0.01, ‡P<0.001.

The hazard ratios (HR) for total mortality for the PCS and MCS were 0.988 (95%CI 0.983-0.993) and 0.990 (95%CI 0.985-0.995), respectively. A 1-point-higher score on the PCS and MCS decreases the risk for mortality with 1.2 and 1.0 %. This means that a clinically meaningful increase of a 10-point-higher score, on a 100-point scale, on the PCS and MCS decreased the risk for mortality with 11% (0.988 to the power 10) and 10%. For cardiovascular mortality, the HRs of PCS and MCS were 0.988 (95%CI 0.977-0.999) and 0.987 (95%CI 0.975-0.999), respectively. Eight out of 9 health dimensions were related to total mortality, and five health dimensions were associated with cardiovascular mortality (table 2).

RAND-36 dimensions	Total mortality Hazard ratio (95%CI)*	Cardiovascular mortality Hazard ratio (95%CI)*
PCS	0.988 (0.983-0.993)	0.988 (0.977-0.999)
MCS	0.990 (0.985-0.995)	0.987 (0.975-0.999)
Physical functioning	0.988 (0.984-0.991)	0.988 (0.979-0.997)
Social functioning	0.992 (0.988-0.996)	0.996 (0.986-1.006)
Role functioning-physical	0.996 (0.993-0.999)	0.995 (0.991-0.999)
Role functioning-emotional	0.997 (0.994-0.999)	0.994 (0.988-0.999)
Mental health	0.993 (0.989-0.998)	0.987 (0.976-0.998)
Bodily pain	0.994 (0.991-0.998)	0.998 (0.989-1.008)
Vitality	0.993 (0.989-0.998)	0.995 (0.984-1.006)
General health perception	0.984 (0.978-0.991)	0.979 (0.962-0.995)
Health change	0.997 (0.992-1.003)	1.008 (0.994-1.022)

Table 2. Relationship between HRQOL and total and cardiovascular mortality. Hazard ratios refer to a 1-point higher score on the RAND-36 dimensions. *Corrected for age, gender, smoking, duration of diabetes, serum creatinine, body mass index, systolic blood pressure, total cholesterol to HDL-cholesterol ratio, macrovascular complications, use of statins, insulin use and urinary albumin creatinine ratio.

Elderly patients (table 3)

PCS and MCS were also inversely associated with mortality in the subgroup of elderly patients (>75 years) with HRs of 0.989 (95%CI 0.981-0.996) and 0.991 (95%CI 0.984-0.999), respectively. For the subgroup of younger patients (≤75 years), HRs for PCS and MCS were 0.987 (95%CI 0.980-0.993) and 0.988 (95%CI 0.981-0.995), respectively. In the subgroup of elderly patients, 3 out of 9 health dimensions were inversely associated with total mortality with lowest HRs for physical functioning and general health perception.

RAND-36 dimensions	**Total mortality** *> 75years* Hazard ratio (95%CI)*	**Total mortality** *≤ 75 years* Hazard ratio (95%CI)*
PCS	0.989 (0.981-0.996)	0.987 (0.980-0.993)
MCS	0.991 (0.984-0.999)	0.988 (0.981-0.995)
Physical functioning	0.985 (0.979-0.992)	0.988 (0.983-0.993)
Social functioning	0.992 (0.987-0.997)	0.990 (0.985-0.996)
Role functioning-physical	0.997 (0.993-1.000)	0.994 (0.991-0.998)
Role functioning-emotional	0.998 (0.994-1.001)	0.996 (0.992-0.999)
Mental health	0.995 (0.988-1.003)	0.992 (0.985-0.999)
Bodily pain	0.995 (0.989-1.000)	0.993 (0.988-0.998)
Vitality	0.996 (0.989-1.003)	0.992 (0.986-0.998)
General health perception	0.983 (0.973-0.994)	0.984 (0.975-0.993)
Health change	0.997 (0.987-1.006)	0.999 (0.991-1.006)

Table 3. Relationship between HRQOL and total mortality stratified according to age. Hazard ratios refer to a 1-point higher score on the RAND-36 dimensions. *Corrected for age, gender, smoking, duration of diabetes, serum creatinine, body mass index, systolic blood pressure, total cholesterol to HDL-cholesterol ratio, macrovascular complications, use of statins, insulin use and urinary albumin creatinine ratio.

Gender-related differences (table 4)

We found a significant interaction between mental health and gender (p=0.042). After adding the interaction term between gender and mental health to the model, the association between mental health and total mortality became more pronounced, HR 0.976 (95%CI 0.960-0.994). The PCS and MCS were inversely associated with total mortality for both women and men. For female patients the HRs were 0.988 (95% CI 0.982-0.994) and 0.992 (95%CI 0.985-0.998) for PCS and MCS, respectively. For male patients the HRs for PCS and MCS were 0.988 (95%CI 0.981-0.996) and 0.987 (95%CI 0.979-0.995).

A total of 6 out of the 9 health dimensions were related to total mortality for women and 5 out of 9 for men. There were three differences: role physical was significantly related to mortality in women but not in men and bodily pain was significantly related to women but not in men, although absolute HRs did not really differ. Mental health was significantly related to mortality in men but not in women, with also notable differences in HR: 0.984 (95%CI 0.976-0.992) vs.

0.998 (95%CI 0.992-1.004). When looking at the individual 5 questions from which the mental health dimension is composed, all 5 relating to depression and anxiety, these 5 questions were related to mortality in men but none in women (data not shown).

Analysing of the model with the variable "incomplete questionnaire" (instead of the RAND-36 scores), patients who did not complete the RAND-36 had an increased total mortality risk compared to patients who completed the questionnaire. When excluding the first two years of follow-up, the relationship between the two component summaries and total and cardiovascular mortality was still present and did not relevantly change (data not shown). Survival was also predicted by the factors age, gender, serum creatinine and albumin-creatinine ratio. The proportional hazard assumptions were met for all analyses.

	Total mortality *Males*	**Total mortality** *Females*
RAND-36 dimensions	Hazard ratio (95%CI)*	Hazard ratio (95%CI)*
PCS	0.988 (0.981-0.996)	0.988 (0.982-0.994)
MCS	0.987 (0.979-0.995)	0.992 (0.985-0.998)
Physical functioning	0.988 (0.983-0.994)	0.988 (0.982-0.993)
Social functioning	0.990 (0.984-0.996)	0.993 (0.988-0.998)
Role functioning-physical	0.997 (0.993-1.001)	0.996 (0.993-0.999)
Role functioning-emotional	0.996 (0.992-1.001)	0.997 (0.994-1.000)
Mental health	0.984 (0.976-0.992)	0.998 (0.992-1.004)
Bodily pain	0.994 (0.989-1.000)	0.994 (0.989-0.999)
Vitality	0.993 (0.987-0.999)	0.993 (0.988-0.999)
General health perception	0.986 (0.976-0.996)	0.983 (0.974-0.992)
Health change	0.998 (0.989-1.006)	0.997 (0.989-1.004)

Table 4. Relationship between HRQOL and total mortality stratified according to gender. Hazard ratios refer to a 1-point higher score on the RAND-36 dimensions. *Corrected for age, smoking, duration of diabetes, serum creatinine, body mass index, systolic blood pressure, total cholesterol to HDL-cholesterol ratio, macrovascular complications, use of statins, insulin use and urinary albumin creatinine ratio.

Discussion

After a median follow-up period of almost ten years, total and cardiovascular mortality was increased for T2DM patients who had a lower HRQOL at baseline. Both the Physical and Mental Component Summaries (PCS and MCS) were related to total and cardiovascular mortality regardless of confounders such as age and gender. A 10-point-higher score, on a 100-point scale, on the PCS and MCS decreased the risk for mortality with 11% and 10%. These effects appear to be clinically relevant and comparable with a 1% decrease in HbA1c (18). Our study supports the recommendations to include measurement and integration of health status in clinical practice (19,20). As it is difficult to interpret the applicability of our results for daily

practice, we present an example: if a female patient has a score of 40 on the PCS, this means that her absolute score is 10 points lower than the mean (using the T-score transformation the PCS has a mean of 50). Her HR for mortality would be 11.4 % higher (0.988 to the power of 10).

In our previous study, which had a median follow-up period of 5.8 years, the only significant association we found was between the PCS score and total mortality, and two separate health dimensions: 'physical functioning' and 'general health perception' (6). The association between the MCS score and mortality was 1.008 (CI 0.994-1.022). In our present study, with almost 10 years of follow-up, the relationship is quite different, and MCS is now inversely associated with mortality. This may imply that low MCS scores can only predict mortality after a longer follow-up period. Furthermore, the relationships between the separate health dimensions and mortality have become more pronounced, with most dimensions being inversely related to mortality.

For the gender specific analysis, an interesting interaction between mental health and gender existed. Such an interaction could mean that gender has an effect on the relationship between mental health and mortality. Stratification for gender revealed one relevant difference: 'mental health' was related to mortality in men only. A 10-point-higher score on the dimension mental health decreased mortality risk with 15% in men. At baseline, women rated their mental health worse compared to men with a median score of 79 versus 71 in men (p=0.001). Patients with decreased scores on the mental health dimension have symptoms related to depression and anxiety (21). This difference between men and women in our cohort could imply that poorer mental health, although less prevalent in men compared to women, has a greater effect on mortality in men. The individual questions from which the mental health dimension is composed are related to depression and anxiety and there is some evidence in a non-diabetic population that depression effects mortality risk in men more than in women (22).

In the age specific analysis in which we stratified for age, many associations were not significant for patients aged >75 years. However, these differences do not seem to be clinically relevant, and are probably caused by the reduction in sample size after stratification. According to the various subgroup analyses, the health dimensions 'physical functioning', 'social functioning', and 'general health' were the most consistent predictors for mortality. Previous studies have shown that a patient's self-rated health status is consistently associated with mortality (23,24).

Due to this study's observational design, it is not clear whether there is a true causal relationship between HRQOL and mortality. The question remains whether HRQOL is a modifiable risk factor or just a marker of disease burden. No randomized controlled trials have been performed in which an attempt was made to specifically improve HRQOL. Whether HRQOL

is a causal factor for mortality, we first would need to identify a possible treatment strategy to improve HRQOL. A recent meta-analysis could not identify psychosocial interventions with clinically relevant benefit with regard to physical and mental health in patients with diabetes [25]. Developing such strategies remains an important challenge and could have implications for the understanding of interaction between physical and mental health. Patients with diabetes are also more prone to depression compared with patients without diabetes (26). The dimension mental health is correlated to depression (13) and depression is independently associated with a lower HRQOL and mortality (26), hence one could hypothesize that treating a depression, and indirectly HRQOL, may increase survival. Such a hypothesis needs to be investigated, however. Several trials have been performed in depressed patients following a myocardial infarction, but all interventions applied did not increase survival (27).

There are additional limitations to our study. 22% of our patient population did not complete the RAND-36 questionnaire. As not completing the questionnaire was associated with an increased mortality, it is likely that the relationships between the HRQOL indices and (cardiovascular) mortality are underestimated in this study. There may also be additional confounders, such as depression and social economic status, which we did not take into account and which may, therefore, have influenced the outcome (26). Furthermore, no adjustment were made for a history of diseases other than cardiovascular disease. However, after excluding the first two years of follow-up from the analysis, the relationship between HRQOL and (cardiovascular) mortality remained largely unchanged. Excluding the first two years of follow-up could correct for severe co-morbidity or undiagnosed cancer at the start of the study, which could have influenced outcome.

Specific strengths of our study include the prospective nature of the design and a follow-up period of almost ten years. The number of deaths after the ten years period was sufficient to allow reliable estimates of associations with mortality. We also performed a T-score transformation which has the advantage of permitting comparisons of mean scores for health in different countries (16).

Our study shows that a decrease in HRQOL is associated with an increase in (cardiovascular) mortality among young as well as elderly T2DM patients. HRQOL instruments may become an increasingly useful clinical tool to not only identify those patients with a low HRQOL but also to identify those patients with an associated increase in mortality risk. This study supports the clinical predictive use of HRQOL measures in combination with the well established risk factors for the assessment of mortality risk for patients with T2DM.

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Chapter 8

Orthostatic hypotension, diabetes and falling in elderly subjects: a cross-sectional study

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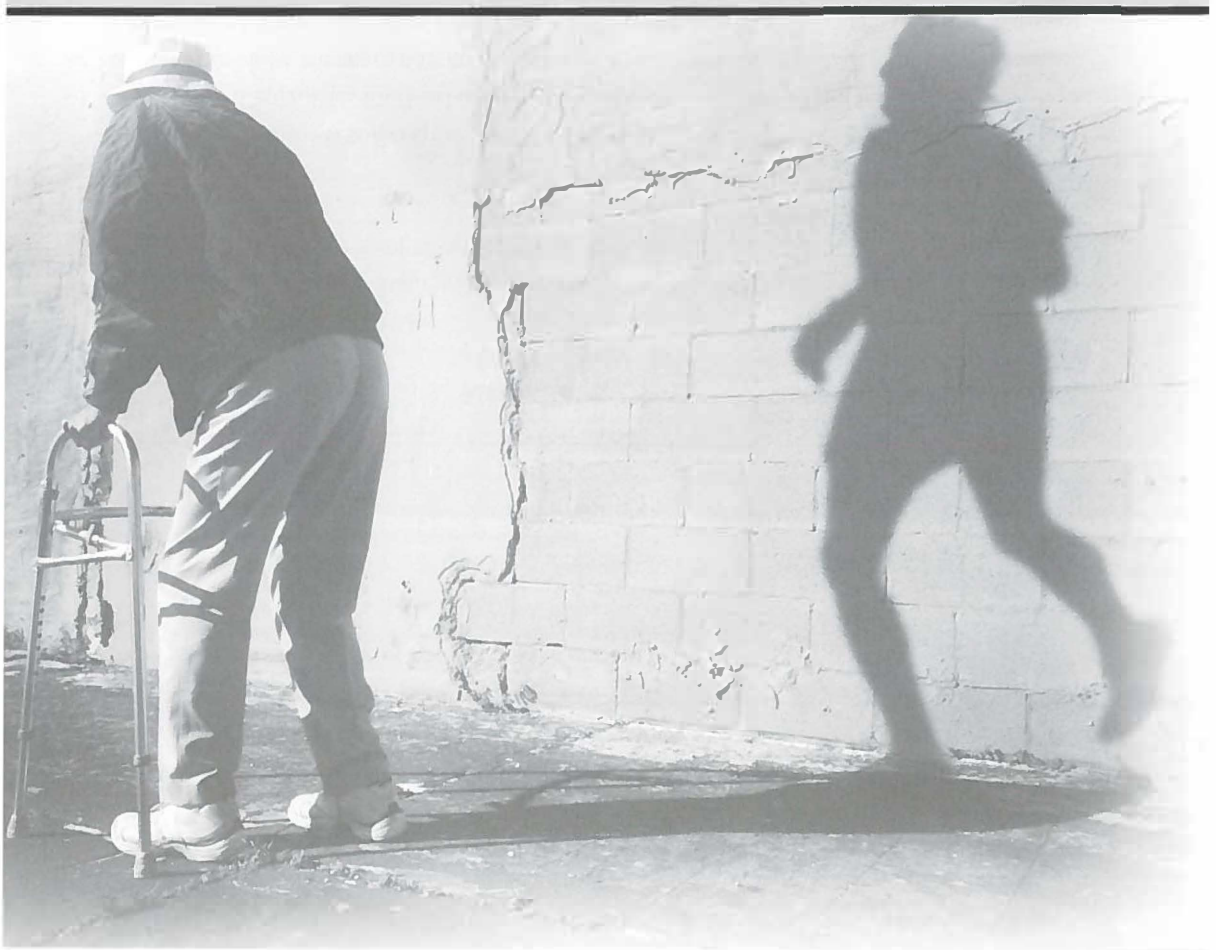

Abstract

Objective: Although orthostatic hypotension (OH) is more prevalent in old age, and in patients with diabetes, the prevalence of OH in elderly patients with T2DM is unknown.

Aim: To establish the prevalence of OH, and its association with falling, in home-dwelling elderly subjects with and without type 2 diabetes mellitus (T2DM).

Design: Cross-sectional study.

Setting: Primary care, the Netherlands.

Method: A total of 352 patients with, and 211 subjects without T2DM participated in this study. OH was defined as a fall in blood pressure of at least 20 mmHg systolic or 10 mmHg diastolic after either one or three minutes in upright position. Feelings of dizziness, light-headedness or faintness during the standing period were documented as orthostatic complaints. Fall risk was assessed with a validated risk profile instrument.

Results: The prevalence of OH was 28% (95%CI 24%-33%) and 18% (95%CI 13%-23%) in subjects with and without T2DM, respectively. OH was not related to falling, while the presence of orthostatic complaints in itself was associated with both previous fall incidents as well as a high fall risk, even after adjustment for OH. The adjusted odds ratios were 1.65 (95%CI 1.00-2.72) and 8.21 (95%CI 4.17-16.19), respectively.

Conclusion: OH is highly prevalent in home-dwelling elderly patients with and without T2DM. Patients with orthostatic complaints had an increased risk for falling, whereas patients with OH were not.

Trial registration: Clinicaltrials.gov number, NCT00807976.

Introduction

Orthostatic hypotension (OH) is increasingly recognised as an important risk factor for cardiovascular disease and mortality [1-5]. Many fall prevention programs are based on the assumed association between OH and falling, although the evidence regarding this association is conflicting [6-12]. The reported prevalence of OH varies widely in literature, probably because its presence is influenced by many factors, including setting, age, definitions of OH, medications used and co-morbidity [6,13,14]. In patients with diabetes, OH is considered to be a clinical manifestation of diabetic autonomic neuropathy. However, other risk factors for OH, such as hypertension and cardiovascular disease, also cluster in patients with type 2 diabetes mellitus (T2DM). The estimated prevalence of OH in home-dwelling elderly, aged 70 years and older, is approximately 30% [1,15,16]. Although OH is more prevalent in old age [6], and in patients with diabetes [17], the actual prevalence of OH in elderly patients with T2DM is unknown.

The primary objective of this cross-sectional study was to establish the prevalence of OH in home-dwelling elderly patients with T2DM. Investigating associated factors of OH, and the prevalence of OH in patients without T2DM were secondary objectives. Because of the high fall rate in older people, especially in those with diabetes [18], and the conflicting evidence whether OH should be considered a risk factor for falling, we were also specifically interested in the association of OH with fall incidents and fall risk.

Methods and patients

Study population

The patients with T2DM participating in our cross-sectional observational study were recruited from 35 general practices, predominantly located in the North Eastern region of the Netherlands. Recruitment and all study procedures took place between January 2009 and May 2010. Eligible diabetic patients were either selected by practice nurses during the periodical diabetic check-up, or by the investigators using the general practitioners' patients information systems. All participating nurses were visited and trained by the investigators for trial procedures. The initial selection included patients with a diagnosis of T2DM, aged 70 years or older, and the ability to follow the study protocol. Exclusion criteria were: (1) known autonomic dysfunction, (2) neurodegenerative diseases, (3) active malignancy, (4) irregular pulse, and (5) residing in a nursing home. Patients with irregular pulse were excluded because of the difficulty establishing 'real' OH in these patients, due to the high variability of blood pressure. Subjects in the control group, with no history of diabetes, were selected from 7 out of the 35 general practices. These subjects were either selected during a consultation with the general practitioner, or by the

investigators using the general practitioners' patient information systems. The same selection criteria as in the diabetes group were used. For the patients in the control group selected by using the patients information system, we used one additional criterion: a consultation with the general practitioner in the last six months. We used this criterion in order to select a group that would be comparable to the patients who were selected during a consultation with the general practitioner. The subjects who were selected using the general practitioners' patient information systems, were sent an invitation to participate in our study.

Data collection

Demographic characteristics, medical history, and medication use were assessed using a standard structured questionnaire. The risk of falling was measured using a self-administered validated risk profile developed to identify community-dwelling elderly at high risk of recurrent falling [19]. This risk profile assesses fall risk on the basis of previous fall incidents, body weight, functional limitations, handgrip strength, use of alcohol, presence of pets, level of education and fear of falling. A high risk of falling was defined as a score of 10 points or higher on the risk profile and can be interpreted as a 50% chance of falling at least twice in the upcoming three years.

Measurements were performed by either the investigators or the practice nurses. Height, body weight, and blood pressure were measured in all participating subjects. All subjects were asked whether they had consumed a meal or drink within two and one hours, respectively, prior to the measurements. Blood pressure was measured following a standardised protocol, using a validated A&D digital blood pressure monitor, model UA-767 plus 30 [20]. Two supine measurements were performed after 5 minutes of rest, followed by two measurements after one minute standing and two measurements after three minutes standing. Mean values of the baseline, 1-minute and 3-minute measurements were calculated. During standing, the forearm of the subject was supported at heart level on an adjustable table or on the shoulder of the sitting investigator [21]. The definition of OH was a fall in blood pressure of at least 20 mmHg systolic or 10 mmHg diastolic after either one or three minutes of standing after the subject changed from the supine to the upright position [22,23]. After orthostatic testing, the subjects were asked about feelings of dizziness, light-headedness or faintness during standing (orthostatic complaints).

Statistical analyses

Based on an estimated prevalence of OH of 30%, the required sample size to obtain a 95% confidence interval +/- 5% around the estimated prevalence, was 341 subjects. We aimed to include 350 subjects with T2DM and at least 150 participants in the control group.

First, univariate binary logistic regression analyses were performed to assess the association of the baseline characteristics with OH and orthostatic complaints. Multiple binary logistic regression analyses were performed to assess the association between OH, orthostatic complaints and T2DM. In model 1, we adjusted for age and gender. In model 2, we additionally adjusted for body mass index (BMI), a history of hypertension, previous macrovascular complications, supine systolic blood pressure, the number of antihypertensives used and consumption of a meal/drink before blood pressure measurement.

Finally, the relationships between OH / orthostatic complaints, and previous fall incidents and high fall risk were investigated in 4 different models, in which fall incidents and high fall risk were the outcome variables. In model 1 we adjusted for OH, in model 2 for orthostatic complaints, in model 3 for OH and orthostatic complaints, and in model 4 for symptomatic OH, defined as OH combined with the presence of orthostatic complaints. In all models we additionally adjusted for the following possible predictors of fall incidents and fall risk: age, gender, BMI, T2DM, previous macrovascular complications and the number of antihypertensives used. Since body weight is part of the risk profile by which fall risk was defined, BMI was not included in the models for high fall risk. All analyses were performed with SPSS version 18 software (SPSS Inc., Chicago, IL, USA).

This study was registered at clinicaltrials.gov, NCT00807976. The manuscript was written based on the 'Strengthening the reporting of observational studies in epidemiology' (STROBE) statement [24].

Ethical approval

This study was approved by the local medical ethics committee. Written informed consent was obtained from all participants.

Results

Study population

A total of 352 diabetic patients and 211 subjects without T2DM participated in this study. The number of participants who initially were invited by either the practice nurses, general practitioners or the investigators, is unknown. This number is only known for the participants we selected ourselves: of the 398 subjects invited to participate, 218 (55%) subjects actually participated. The non-responders were older (78.6 vs. 75.5 years, $p<0.001$), but no significant gender difference between the responders and the non-responders was found (43.6% versus 35.6% males, $p=0.104$).

Baseline characteristics and the results of the univariate regression analyses are presented in table 1. Both macrovascular complications and the total number of drugs were univariate associated with OH and orthostatic complaints. Experiencing orthostatic complaints was related to a higher risk of OH. Higher blood pressure and not having consumed a meal or drink were associated with a higher prevalence of OH, but not with the presence of orthostatic complaints. Being female, hypertension, previous fall incidents, a higher score on the risk profile, a high fall risk and the number of antihypertensive agents were only related to experiencing orthostatic complaints.

Characteristic (n = 563)		**Odds ratio (95%CI)**	
		OH	*Orthostatic complaints*
Demographics			
- Age (years)	75 (72-79)	0.99 (0.95-1.03)	0.99 (0.95-1.05)
- Male sex	265/563 (47.1)	1.06 (0.72-1.56)	0.56 (0.35-0.91)
- Body mass index (kg/m^2)	28.0 (4.2)	0.97 (0.93-1.02)	1.00 (0.95-1.06)
- Type 2 diabetes mellitus (T2DM)	352/563 (62.5)	1.87 (1.22-2.85)	2.16 (1.27-3.69)
- Duration of T2DM (years)	6 (4-10)	1.00 (0.96-1.05)	1.00 (0.96-1.05)
- Hypertension	438/563 (77.8)	1.37 (0.84-2.24)	2.11 (1.08-4.11)
- Macrovascular complications	175/563 (31.1)	1.71 (1.15-2.56)	2.13 (1.33-3.41)
- Family history of CVD	141/563 (25.0)	1.09 (0.70-1.69)	1.05 (0.62-1.79)
Measurements			
- Consumption meal/drink	394/558 (70.6)	0.40 (0.27-0.60)	0.82 (0.50-1.35)
- Systolic BP lying (mm Hg)	142.1 (20.5)	1.31 (1.19-1.44)	0.89 (0.79-1.00)
- Diastolic BP lying (mm Hg)	76.1 (9.9)	1.33 (1.09-1.62)	0.85 (0.67-1.08)
- Pulse frequency	67.0 (10.8)	0.99 (0.97-1.01)	1.00 (0.98-1.02)
- Fall incidents in previous year	169/553 (30.6)	0.97 (0.64-1.49)	1.79 (1.11-2.88)
- Score risk profile	3 (1-6)	1.02 (0.97-1.08)	1.26 (1.19-1.33)
- High fall risk	47/561 (8.4)	0.95 (0.47-1.92)	8.60 (4.57-16.19)
- Orthostatic complaints	85/563 (15.1)	2.02 (1.23-3.29)	NA
Medication			
- Number of pharmacological agents	5 (3-6)	1.12 (1.04-1.20)	1.17 (1.08-1.27)
- Number of antihypertensive agents	2 (0-3)	1.14 (0.99-1.32)	1.19 (1.01-1.41)
- Antihypertensive treatment	418/563 (74.2)	1.39 (0.88-2.21)	1.74 (0.96-3.15)

Table 1. Baseline characteristics and results of univariate logistic regression analyses with orthostatic hypotension (OH) and orthostatic complaints as dependent variables. Data are means (SD), medians (interquartile range) or *n* (%). A high risk of falling was defined as a score of 10 points or higher on the risk profile and can be interpreted as a 50% chance of falling twice or more often in the upcoming three years. The odds ratios for systolic and diastolic blood pressure refer to a pressure increase of 10 mm Hg. NA = not applicable.

T2DM and OH

The prevalence of OH was 28% (95%CI 24%-33%) and 18% (95%CI 13%-23%) in subjects with and without T2DM, respectively. The results from the multivariate logistic regression analyses, as presented in table 2, show that the association between T2DM and OH is independent from other clinical variables. In these models, a history of macrovascular complications, higher supine systolic blood pressure, and no consumption of a meal/drink before measurements were also independently associated with a higher risk of OH. The prevalence of orthostatic complaints was 18% (95%CI 15%-23%) and 10% (95%CI 6%-14%) in subjects with and without T2DM, respectively. In multivariate analyses, the association between orthostatic complaints and T2DM was confirmed. Female gender, a history of macrovascular complications and lower supine systolic blood pressure increased the risk of orthostatic complaints.

	Orthostatic hypotension		***Orthostatic complaints***	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Variables	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*
T2DM, DM vs control	1.89 (1.23-2.90)	1.89 (1.16-3.08)	2.34 (1.36-4.02)	2.08 (1.17-3.72)
Age	0.99 (0.94-1.03)	0.95 (0.91-1.00)	0.98 (0.93-1.04)	0.98 (0.93-1.03)
Gender, male vs female	1.00 (0.68-1.48)	0.97 (0.63-1.50)	0.52 (0.32-0.85)	0.38 (0.23-0.65)
Body Mass Index	-	0.95 (0.90-1.01)	-	0.96 (0.91-1.03)
Hypertension	-	0.85 (0.42-1.69)	-	1..78 (0.75-4.24)
Macrovascular complications	-	2.14 (1.33-3.45)	-	2.29 (1.33-3.92)
Systolic blood pressure	-	1.33 (1.20-1.48)	-	0.87 (0.76-0.98)
Antihypertensives	-	1.03 (0.84-1.27)	-	0.93 (0.74-1.19)
Consumption meal/drink	-	0.46 (0.30-0.72)	-	0.76 (0.45-1.29)

Table 2. Adjusted odds ratios for the effects of clinical variables on the risk of orthostatic hypotension and orthostatic complaints. The odds ratios for systolic blood pressure refer to a pressure increase of 10 mm Hg. The odds ratios can be interpreted as a measure of the association of the various variables to either orthostatic hypotension or orthostatic complaints (the dependent variables).

Fall incidents and fall risk

Tables 3 and 4 present the multivariate regression analyses with previous fall incidents and high fall risk as the dependent variables. OH was not related to previous fall incidents and high fall risk, in both univariate (data not shown) and multivariate analyses. The unadjusted odds ratios of orthostatic complaints for fall incidents and high fall risk were 1.79 (95%CI 1.11-2.88) and 8.60 (4.57-16.19), respectively. In multivariate analyses, the odds ratios were 1.63 (95%CI 0.99-2.68) and 7.77 (95%CI 3.98-15.17). After additionally adjusting for OH, orthostatic complaints remained associated with previous fall incidents and a high fall risk. Female gender was independently related to previous fall incidents. Higher age was associated with high fall risk only.

	Previous fall incidents as the dependent variable			
	Model 1	**Model 2**	**Model 3**	**Model 4**
	Odds ratio (95% CI)	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*
OH	0.94 (0.61-1.46)	-	0.90 (0.58-1.40)	-
Orthostatic complaints	-	1.63 (0.99-2.68)	1.65 (1.00-2.72)	-
Symptomatic OH	-	-	-	1.99 (0.93-4.23)
Age	1.02 (0.98-1.07)	1.03 (0.98-1.07)	1.02 (0.98-1.07)	1.03 (0.98-1.07)
Gender, male vs female	0.50 (0.34-0.75)	0.53 (0.36-0.79)	0.53 (0.36-0.78)	0.53 (0.36-0.78)
Body Mass Index	0.98 (0.93-1.03)	0.98 (0.94-1.03)	0.98 (0.94-1.03)	0.98 (0.94-1.03)
T2DM, DM vs control	1.08 (0.72-1.62)	1.02 (0.68-1.54)	1.03 (0.68-1.55)	1.06 (0.71-1.59)
Macrovascular complications	1.06 (0.68-1.64)	0.99 (0.64-1.54)	1.00 (0.64-1.56)	0.99 (0.64-1.54)
Antihypertensives	1.07 (0.92-1.25)	1.07 (0.91-1.25)	1.07 (0.92-1.25)	1.07 (0.92-1.25)

Table 3. Adjusted odds ratios for the effect of clinical variables on the risk of previous fall incidents. In model 1 we adjusted for OH, in model 2 for orthostatic complaints, in model 3 for OH and orthostatic complaints, and in model 4 for symptomatic orthostatic hypotension. In all models we additionally adjusted for the following possible predictors of fall incidents: age, gender, BMI, T2DM, previous macrovascular complications and the number of antihypertensives used. The odds ratios can be interpreted as a measure of the association of the various variables to either previous fall incidents or high fall risk (the dependent variables).

	High fall risk as the dependent variable			
	Model 1	**Model 2**	**Model 3**	**Model 4**
	Odds ratio (95% CI)	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*
OH	0.80 (0.38-1.65)	-	0.61 (0.28-1.34)	-
Orthostatic complaints	-	7.77 (3.98-15.17)	8.21 (4.17-16.19)	-
Symptomatic OH	-	-	-	2.87 (1.09-7.55)
Age	1.07 (1.01-1.14)	1.09 (1.02-1.16)	1.09 (1.02-1.16)	1.07 (1.01-1.14)
Gender, male vs female	0.47 (0.24-0.92)	0.61 (0.30-1.23)	0.59 (0.29-1.20)	0.53 (0.27-1.04)
T2DM, DM vs control	1.75 (0.83-3.68)	1.38 (0.64-2.98)	1.39 (0.65-3.01)	1.69 (0.80-3.56)
Macrovascular complications	1.61 (0.82-3.17)	1.16 (0.57-2.39)	1.24 (0.60-2.57)	1.39 (0.70-2.77)
Antihypertensives	1.20 (0.94-1.54)	1.21 (0.94-1.57)	1.21 (0.94-1.57)	1.21 (0.94-1.55)

Table 4. Adjusted odds ratios for the effect of clinical variables on the risk of high fall risk. In model 1 we adjusted for OH, in model 2 for orthostatic complaints, in model 3 for OH and orthostatic complaints, and in model 4 for symptomatic orthostatic hypotension. In all models we additionally adjusted for the following possible predictors of fall incidents: age, gender, T2DM, previous macrovascular complications and the number of antihypertensives used. BMI was not included in the models since body weight is used in the risk profile by which high fall risk was defined. The odds ratios can be interpreted as a measure of the association of the various variables to either previous fall incidents or high fall risk (the dependent variables).

Discussion

The prevalence of OH in elderly home-dwelling patients with T2DM was 28%, which was significantly higher than the prevalence of 18% in the patients without T2DM. Besides T2DM, we also found independent associations with a history of macrovascular complications, higher systolic blood pressure and no consumption of a meal/drink before orthostatic testing. OH was not related to either previous fall incidents or a high fall risk. Remarkably, only the presence of orthostatic complaints was associated with more fall incidents and an increased risk of falling, even after adjustment for OH. Orthostatic complaints were more prevalent in patients with T2DM or cardiovascular disease, and in female patients.

In previous reports, the prevalence of OH in home-dwelling elderly, aged 70 years and older, was estimated to be approximately 30% in the general population [1,15,16]. This is comparable to the prevalence in type 2 diabetic patients observed in our study. However, the prevalence in our control group was much lower. Higher mean age, lower BMI, and higher blood pressure may be the explanations for the higher prevalence of OH observed in previous studies [1,15,16]. Only one previous population-based study specifically investigated the prevalence of OH in T2DM before, and reported a prevalence comparable to our study, namely 25.5% [17]. In this study, mean age was lower and much less patients were on antihypertensive medication. All measurements were performed between 8:00 and 10:00 in the morning, unlike in our study in which measurements were performed throughout the day. Since the prevalence of OH is higher when measured in the morning, especially before breakfast, this may have caused an underestimation of the prevalence of OH in our study [25]. The associations we observed between OH and macrovascular complications, higher systolic blood pressure and not having consumed a meal/drink before testing confirm data from previous studies [1,6,17,25].

A prospective study on fall risk showed that withdrawal of cardiovascular drugs led to lower fall risk and a reduction in OH [26,27]. Although a relationship between OH and falling was suggested in this study, causality was not proven. Observational studies show conflicting evidence regarding the association between OH and fall incidents [6-12]. Except for the study by Rutan et al., all other studies, which reported a positive association between falling and OH, were performed in nursing homes or homes for the elderly [6-10]. In the community-based study by Rutan et al. orthostatic testing was only performed after 3 minutes of standing. The age- and clinic-adjusted odds ratio of OH for frequent falls was 1.52 (95%CI 1.04-2.22) in this study [6]. The relationship between OH and fall incidents is probably influenced by many factors, including study population (i.e. nursing home versus community-dwelling elderly) and definition of OH (i.e. blood pressure drop after 1 minute versus blood pressure drop after 1 or 3 minutes). Based on our results, it seems reasonable to suggest that it is not OH, but the

presence of orthostatic complaints that is predictive of previous fall incidents and high fall risk in a home-dwelling elderly population.

The main limitation of our study is potential selection bias. Participants were either selected by practice nurses during the periodical diabetic check-up, or by the investigators using the general practitioners' patient information systems. Since the majority of the patients in the diabetes group were selected by practice nurses (77%), and the majority of the control group by the investigators, this may have led to a selection bias. However, baseline characteristics of patients with T2DM did not differ between those recruited by the practice nurses and those recruited by the investigators (data not presented). Therefore, this gives some reassurance, that differences between the nurses and investigators have not led to an important selection bias. It is also possible that the patients who were willing to participate had some characteristics we could not adjust for in our analyses. Unfortunately, data of the non-responders was only known the participants we selected ourselves. Since the responders in our study were younger than the non-responders, the results on prevalence of OH may be an underestimation. Furthermore, patients with an irregular pulse were excluded from our study. Therefore, our results are not applicable to patients with an irregular pulse/atrial fibrillation.

Another limitation of our study may be the possibility of recall bias. Since we assessed the fall incidents retrospectively, it is very likely that the actual number of fall incidents was higher. Finally, we found a poor correlation between OH and orthostatic complaints. Out of the 137 patients with OH, only 31 patients had typical orthostatic complaints. Perhaps differences in the definition of OH may explain the poor correlation between OH and orthostatic complaints. However, the correlation between OH and orthostatic complaints was not different for various definitions of OH in our study (data not presented). The majority of studies, such as the study by Rutan et al., did not describe either the number of patients with OH and complaints, nor the number of patients experiencing complaints without measuring OH, making it difficult to compare the poor correlation found in our study to those studies [6]. A recently published study using continuous non-invasive orthostatic blood pressure measurements showed that only initial orthostatic hypotension (during the first 15 seconds) was related to orthostatic complaints and falls, whereas this relationship was not found for orthostatic hypotension after 3 minutes [28]. This could also be the explanation for the poor correlation between OH and complaints/falls in our study. Unfortunately, we have not measured blood pressure within the first seconds upon standing in our study.

Our study has some notable strengths. Firstly, we calculated the mean of two blood pressure measurements at baseline, after 1 minute of standing, and after 3 minutes of standing. This allowed us to correct for the imprecision inherent to a single blood pressure measurement.

Secondly, all measurements were performed using the same validated automatic blood pressure monitoring device. Thirdly, unlike many other studies we collected data on consumption of meals or drinks before orthostatic testing.

In conclusion, this study shows that OH is highly prevalent in elderly patients with and without T2DM. Our results suggest that falling is only related to orthostatic complaints, and not to OH. Confirmation in other studies is necessary, and if confirmed, it may be as simple as just asking some questions instead of following a time consuming protocol in order to select those patients with an increased risk of falling.

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Chapter 9

A prospective observational study of quality of diabetes care in a shared care setting: trends and age differences (ZODIAC-19)

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Abstract

Objective: The Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) study was initiated in 1998 to investigate the effects of shared care for patients with type 2 diabetes mellitus (T2DM) in the Netherlands, and to reduce the number of diabetes-related complications. Benchmarking the performance of diabetes care was and is an important aspect of this study. We aimed to investigate trends in diabetes care, within the ZODIAC study for a wide variety of quality indicators during a long follow-up period (1998-2008), with special interest for different age groups.

Design and setting: Prospective observational cohort study. Primary care, Zwolle, The Netherlands.

Participants: Patients with T2DM.

Methods: A dataset of quality measures was collected annually during the patient's visit to the practice nurse or general practitioner. Linear time trends from 1998-2008 were estimated using linear mixed models in which we adjusted for age and gender. Age was included in the model as a categorical variable: for each follow-up year all participants were categorised into the categories <60, 60-75 and >75 years. Differences in trends between the age categories were investigated by adding an interaction term to the model.

Results: The number of patients who were reported to participate increased in the period 1998-2008 from 1622 to 27.438. All quality indicators improved in this study, except for body mass index. The prevalence albuminuria decreased in an eleven-year-period from 42% to 21%. No relevant differences between the trends for the 3 age categories were observed. During all years of follow-up, mean blood pressure and body mass index were the lowest and highest, respectively, in the group of patients <60 years (data not shown).

Conclusion: Quality of diabetes care within the Dutch ZODIAC study, a shared care project, has considerably improved in the period 1998-2008. There were no relevant differences between trends across various age categories.

Introduction

Ever since it was established that type 2 diabetes mellitus (T2DM) leads to significant morbidity and mortality [1,2], prevention and (early) treatment of both microvascular and macrovascular complications of T2DM have become important goals in diabetes care. Efforts to improve the quality of diabetes care are necessary in order to reduce morbidity and mortality associated with T2DM [3,4]. Since adequate treatment of patients with T2DM often needs the involvement of more than one caregiver, shared care, defined as care for patients with a chronic condition provided in cooperation between primary and secondary health care, has been promoted and developed [5].

The *Zwolle Outpatient Diabetes project Integrating Available Care* (ZODIAC) study was initiated in 1998 to investigate the effects of shared care for patients with T2DM in the Netherlands [6]. Benchmarking the performance of diabetes care was and is an important aspect of this initiative. Previous reports from the ZODIAC study showed that structured shared care with task delegation to nurses leads to improvements in quality of diabetes care and life expectancy [6-8]. However, effectiveness of shared care in general was not demonstrated in a 2007 Cochrane review [5]. Inadequate length of follow-up was mentioned by the authors as a possible explanation for the lack of evidence.

Although diabetes care has improved considerably during the past decades in patients with diabetes, there is limited data whether these improvements are comparable across different age categories [9,10]. A cross-sectional study from France showed that quality of care had considerably improved for patients ≥65 years with T2DM in the period 2001-2007 [11]. Unfortunately, trends for patients >75 years were not described separately in this study. Although the number of patients with T2DM >75 years is increasing, the evidence for cardiovascular risk interventions in this age category is low [12]. Data from observational studies show that classic cardiovascular risk factors may even have different consequences in elderly patients [13-17].

In the present study, we aimed to investigate trends in diabetes care, within a shared care project, for a wide variety of quality indicators during a long follow-up period (1998-2008). Because of limited evidence for cardiovascular risk interventions in old age, we had specific interest whether the same trends were observed for different age groups (<60, 60-75 and >75 years).

Methods and Patients

Study population and ZODIAC

The ZODIAC study started in 1998 as a prospective observational study for patients with T2DM [6]. Participating practices were allocated to one of the two intervention groups or to the standard care group. The interventions involved extensive or limited task delegation from general practitioners to practice nurses and/or diabetes specialist nurses. Moreover, it included a diabetes register, structured recall, facilitated generalist-specialist communication, audit and feedback, patient-specific reminders, and it emphasized patients' education [6]. The patients participating in the ZODIAC study are known with T2DM and exclusively treated in primary care. Patients who were already treated in secondary care for their diabetes, patients with a very short life expectancy (including patients with active cancer) and patients with insufficient cognitive abilities were excluded from participation. In the first years of ZODIAC, only patients in the surrounding area of the city of Zwolle participated in the study. Because of the improvements in the quality of diabetes care in the two intervention groups, the shared care project has expanded gradually in the past decade. Firstly, the shared care project became the standard for diabetes care in the entire Zwolle region (2002-2003), and in 2005-2006 the project expanded to the northeast region of the Netherlands. Patients who received standard care in the beginning of the project, switched to shared care in 2002-2003 when the shared care project became the standard for the entire Zwolle region. These patients were included in the current analyses from the moment they switched to shared care. The number of participating general practitioners (GPs) has increased from 53 in 1998 to 459 in 2008. Patient numbers increased from 1622 to 27.438 in this time frame, and nowadays even more than 60.000 patients are participating. A benchmark of annually gathered quality measures of this cohort, based on the guidelines of the Dutch College of General Practitioners and the Dutch Diabetes Federation, has been developed [18].

Data collection

The dataset of quality measures is collected annually during the patient's visit to the practice nurse and/or GP. These quality measures are collected in the general practitioners' patients information systems, and each year the relevant data are uploaded and sent to our diabetes centre for benchmarking and research purposes. At baseline, additional data were collected including a full medical history. The dataset contains many quality measures, including data on cardiovascular risk control, treatment and complications. Distinction is made between process and outcome measures. Process measures indicate whether tests or assessments have been performed, e.g. the number of patients whose HbA1c level has been determined. Outcome measures reflect the results of the assessments, such as the mean systolic blood pressure or the proportion of patients with a systolic blood pressure <140 mm Hg. Table 1 shows an overview of the measures we investigated in this study for each year of follow-up.

Parameter	Process measure	Outcome measure
HbA1c	% of patients measured	mean HbA1c (%)
		% HbA1c < 7.0%
		% HbA1c ≥ 8.5%
Glucose lowering treatment	N.A.	% diet only
		% oral medication only
		% insulin with or without oral medication
Blood pressure	% of patients measured	mean SBP (mm Hg)
		% SBP < 140 mm Hg
Antihypertensive treatment	N.A.	% patients using antihypertensive drugs
Cholesterol-HDL ratio	% of patients measured	mean total cholesterol-HDL ratio
		% total cholesterol-HDL ratio <4
Lipid-lowering drugs	N.A.	% patients using lipid-lowering drugs
Renal function	% of patients with creatinine measurements	mean creatinine (µmol/L)
	% of patients with ACR measurements	% micro-albuminuria
		% macro-albuminuria
BMI	% of patients measured	mean BMI (kg/m²)
		% BMI < 25 kg/m²

Table 1. Overview of the process and outcome measures studied. Abbreviations: N.A.: not applicable; SBP: systolic blood pressure; ACR: albumin-creatinine ratio; BMI: body mass index.

Participating practices were instructed to perform blood pressure measurements in supine position after at least 5 min of rest, and to calculate the mean blood pressure of two recordings for each visit. Laboratory data (HbA1c, serum creatinine and lipid profile) were determined using standard hospital procedures. Until 2005, all procedures were performed in the clinical chemistry laboratory of the Isala Clinics (Zwolle region). Because of the expansion of the project in 2005-2006 to the northeast region of the Netherlands, laboratories of other regions started participating. HbA1c was measured using affinity chromatography *high-performance liquid chromatography* (HPLC, Ultra 2, Trinity Biotech, Kansas City, MO) in the Zwolle region (coefficient of variation approximately 1.5%) [19]. There are differences in the methods used in the various laboratories in the northeast region of the Netherlands. Generally speaking, the variation coefficient has decreased in the study period due to the worldwide standardization of HbA1c measurements and improved techniques. Because of the high number of patients in the last years of the project, it is not likely that differences in the coefficient of variation coefficient have influenced the results.

Statistical analyses

Continuous variables are represented as means and 95% confidence intervals (95% CI) for the normally distributed values. Normality was evaluated using Q-Q plots and histograms. Nominal variables are represented as the proportion of patients together with 95% CIs. The database contained 37.320 unique patients and data of 92.340 unique yearly diabetic check-ups. For

9.279 patients, we only had data of one diabetic check-up. The descriptive statistics were strictly cross-sectional and included observations of all visits (n=92.340). Since cross-sectional outcomes are influenced by changes in population (in- and outmigration), besides changes in quality of care, cross-sectional outcomes tend to overestimate time trends when compared to longitudinal analyses [20]. Therefore, we estimated linear time trends from 1998-2008 using a linear mixed model for continuous variables (SAS PROC MIXED) and a generalized linear mixed model for binary variables (PROC GLIMMIX, using the logit link function) in which we adjusted for age and gender. In all analyses time, age and sex were modelled as fixed effects. Since the estimated linear time trends are based on individual changes over time, data of at least 2 visits were necessary. As a consequence, these longitudinal analyses were based on 83.061 visits of 28.041 patients. Age was included in the model as a categorical variable: for each follow-up year all participants were categorised into the categories <60, 60-75 and >75 years. All time trends were visually inspected and a quadratic time trend was only introduced when such a trend was likely based on the plot. Differences in trends between men and women and the age categories were investigated by adding interaction terms for age and time and sex and time to the model. A significant interaction for age and time means that differences exist between the time trends for the 3 age categories. The same applies for the interaction between sex and time. All analyses were performed with SPSS version 18.0.0 software (SPSS inc., Chicago, Illinois, USA) and with SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

The manuscript was written based on the 'Strengthening the reporting of observational studies in epidemiology' (STROBE) statement [21].

Ethics statement

The ZODIAC study and the informed consent procedure were approved by the local medical ethics committee of the Isala Clinics, Zwolle, the Netherlands. In the first years of ZODIAC, verbal informed consent was obtained from all patients and the consent was documented in the patient's records. According to Dutch law, written informed consent was not necessary for this type of study in 1998. Nowadays, written informed consent is obtained. All data were analysed anonymously.

Results

The number of patients who were reported to participate in this shared care project increased in the period 1998-2008 from 1622 to 27.438. Mean age decreased with time from 68.9 to 67.4 years (p for trend <0.0001). A gradual increase was observed for the proportion of male patients participating in the project. Median diabetes duration remained rather constant at 5 years throughout the whole study period. The proportion of patients aged older than

75 years was 31.0% in 1998 and declined to 26.3% in 2008. The number of patients who did not participate in the study due to short life expectancy of insufficient cognitive abilities is unknown after 1999. The results for all process and outcome measures of each year for the overall study group are presented in table 2.

Process measures

All process measures show a similar trend (table 2): a gradual increase in the first years of the project followed by a decrease in the years 2002 and 2003, an increase in the upcoming two years, followed by a decrease in 2006 again and a rising trend in the process measures in the last two years. Body mass index (BMI), the lipid profile and the ACR were less often measured in patients aged >75 years compared to the younger patients (p for interaction with age for all variables <0.0001). Figure 1 illustrates the trends for the process measure of ACR, BMI and blood pressure in the total study population.

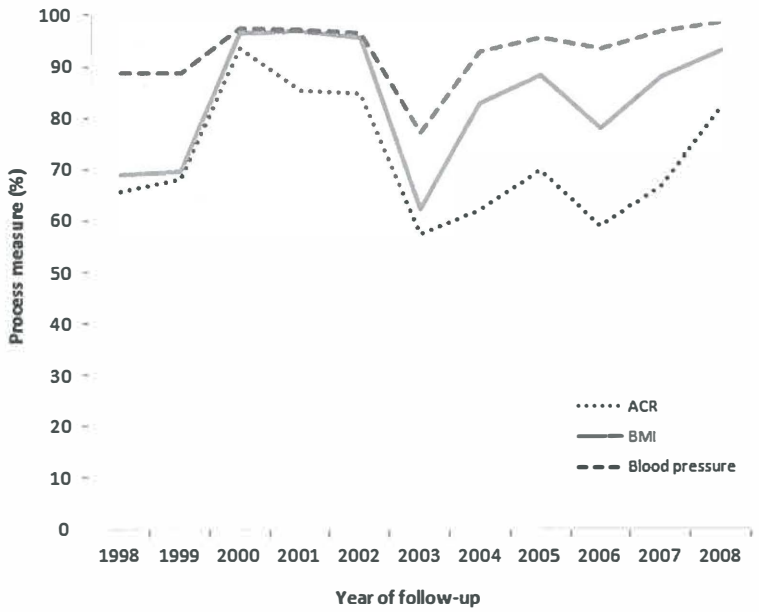


Figure 1. Process measures for albumin-creatinine ratio (ACR), body mass index (BMI) and blood pressure.

		1998 n=1622	1999 n=1767	2000 n=1462	2001 n=1615	2002 n=1761
Age		68.9 (68.4;69.5)	68.9 (68.3;69.4)	67.8 (67.2;68.4)	67.8 (67.2;68.3)	67.0 (66.5;67.6)
Sex (female)		58.0 (55.6;60.4)	58.2 (55.9;60.5)	56.2 (53.7;58.8)	56.9 (54.5;59.3)	55.4 (53.1;57.7)
DM duration		5.2 [2.5;9.8]	5.7 [3.0;10.5]	5.6 [2.8;10.4]	5.0 [2.1;9.9]	4.5 [2.1;9.0]
HbA1c	process	88.6 (87.0;90.1)	86.4 (84.8;88.0)	97.4 (96.6;98.2)	91.1 (89.7;92.5)	91.6 (90.3;92.9)
	mean	7.5 (7.4;7.5)	7.5 (7.4;7.5)	7.3 (7.2;7.3)	7.0 (7.0;7.1)	7.1 (7.0;7.1)
	% <7	40.4 (37.9;43.0)	40.6 (38.1;43.1)	46.6 (44.0;49.2)	56.7 (54.2;59.2)	53.3 (50.9;55.8)
	% ≥8.5	13.2 (11.5;15.0)	12.9 (11.2;14.6)	9.7 (8.2;11.2)	7.8 (6.5;9.2)	7.4 (6.2;8.7)
DM treatment	Diet only	16.6 (14.9;18.5)	18.5 (16.8;20.4)	18.5 (16.6;20.6)	18.2 (16.4;20.2)	23.1 (21.2;25.1)
	% OBLD only	67.9 (65.6;70.2)	65.9 (63.6;68.0)	65.7 (63.3;68.1)	65.0 (62.6;67.2)	61.5 (59.2;63.8)
	% insulin	15.5 (13.8;17.3)	15.6 (14.0;17.4)	15.7 (14.0;17.7)	16.8 (15.1;18.7)	15.4 (13.8;17.2)
SBP	process	88.7 (87.2;90.3)	88.5 (87.0;90.0)	97.3 (96.4;98.1)	97.0 (96.1;97.8)	96.4 (95.5;97.2)
	mean	154.5 (153.3;155.8)	150.3 (149.1;151.4)	149.4 (148.2;150.6)	145.9 (144.9;146.9)	144.4 (143.4;145.4)
	% <140	22.0 (19.9-24.2)	26.4 (24.2;28.6)	29.4 (27.0;31.8)	33.0 (30.7;35.3)	34.6 (32.4;36.9)
SBP treatment	% drugs	41.1 (38.8;43.5)	49.6 (47.3;52.0)	55.0 (52.4;57.5)	61.1 (58.7;63.5)	65.7 (63.4;67.9)
Chol-HDL Ratio	process	73.3 (71.2;75.5)	74.9 (72.9;77.0)	96.4 (95.4;97.3)	91.9 (90.6;93.2)	92.3 (91.0;93.5)
	mean	5.2 (5.1;5.3)	4.8 (4.7;4.9)	4.5 (4.5;4.6)	4.4 (4.3;4.5)	4.1 (4.0;4.1)
	% <4	23.0 (20.7;25.4)	30.7 (28.2;33.1)	35.6 (33.1;38.1)	42.3 (39.8;44.8)	49.8 (47.4;52.3)
LLD	% drugs	10.2 (8.9;11.8)	13.5 (12.0;15.2)	20.8 (18.8;23.0)	26.2 (24.1;28.4)	29.9 (27.8;32.1)
Creatini	process	89.1 (87.6;90.7)	87.3 (85.8;88.9)	97.5 (96.7;98.3)	91.9 (90.6;93.2)	91.8 (90.5;93.1)
	mean	96.5 (51.7;141.2)	95.0 (48.9;141.1)	93.8 (50.2;137.4)	96.8 (52.9;140.7)	98.2 (54.4;142.0)
ACR	process	65.8 (63.5;68.2)	68.0 (65.9;70.2)	93.5 (92.2;94.8)	85.4 (83.7;87.1)	84.8 (83.2;86.5)
	% micro	33.6 (30.8;36.4)	32.6 (30.0;35.3)	31.4 (28.9;33.8)	29.4 (27.0;31.8)	25.1 (22.9;27.3)
	% macro	8.3 (6.7;10.0)	7.7 (6.2;9.2)	6.7 (5.3;8.0)	4.7 (3.6;5.8)	4.8 (3.7;5.9)
BMI	process	69.0 (66.7;71.2)	69.5 (67.3;71.6)	96.9 (96.0;97.7)	96.7 (95.8;97.5)	95.7 (94.8;96.7)
	mean	29.0 (28.7;29.2)	28.9 (28.6;29.1)	29.3 (29.0;29.5)	29.4 (29.2;29.7)	29.5 (29.3;29.7)
	% <25	20.4 (18.0;22.7)	20.4 (18.1;22.6)	17.4 (15.5;19.4)	16.7 (14.8;18.5)	15.8 (14.0;17.5)

Table 2. Characteristics of all participants in the ZODIAC study for the period 1998-2008. All data are mean values or proportions together with their 95% confidence intervals, or median values together with the interquartile range. * P for trend is based on age- and gender-adjusted analyses. Abbreviations: DM: diabetes mellitus, OBLD: oral blood glucose lowering drugs, SBP: systolic blood pressure, LLD: lipid lowering drugs, MDRD: modification of diet in renal disease, ACR: albumin-creatinine ratio, BMI: body mass index.

2003 n=4029	2004 n=4729	2005 n=4508	2006 n=18469	2007 n=24940	2008 n=27438	*P for trend**
67.6 (67.2;67.9)	67.5 (67.2;67.9)	67.5 (67.2;67.8)	67.4 (67.2;67.6)	67.0 (66.9;67.2)	67.4 (67.2;67.5)	<0.0001
54.7 (53.2;56.2)	53.8 (52.4;55.2)	53.5 (52.1;55.0)	52.6 (51.9;53.3)	52.6 (51.9;53.2)	51.9 (51.3;52.5)	<0.0001
4.5 [2.3;8.5]	4.9 [2.3;8.5]	5.0 [2.6;8.7]	4.7 [2.4;8.1]	4.8 [2.4;8.1]	5.3 [2.9;8.8]	<0.0001
83.6 (82.5;84.8)	85.9 (84.9;86.8)	96.1 (95.5;96.6)	87.8 (87.3;88.3)	85.8 (85.4;86.2)	95.5 (95.3;95.8)	<0.0001
7.0 (6.9;7.0)	7.0 (7.0;7.0)	6.8 (6.8;6.9)	6.7 (6.7;6.8)	6.7 (6.7;6.7)	6.7 (6.7;6.7)	<0.0001
57.2 (55.5;58.8)	57.0 (55.5;58.5)	61.9 (60.5;63.4)	67.5 (66.8;68.2)	69.8 (69.2;70.5)	70.1 (69.6;70.7)	<0.0001
5.7 (4.9;6.5)	5.6 (4.9;6.3)	3.4 (2.8;3.9)	3.0 (2.8;3.3)	2.6 (2.4;2.8)	2.3 (2.1;2.5)	<0.0001
21.9 (20.7;23.2)	21.3 (20.1;22.5)	20.1 (18.9;21.3)	24.1 (23.5;24.7)	24.9 (24.3;25.4)	23.8 (23.3;24.3)	<0.0001
64.5 (63.0;66.0)	62.1 (60.7;63.5)	63.0 (61.6;64.4)	63.8 (63.1;64.4)	62.8 (62.2;63.4)	63.4 (62.9;64.0)	<0.0001
13.6 (12.5;14.6)	16.6 (15.6;17.7)	16.9 (15.9;18.1)	12.2 (11.7;12.6)	12.3 (11.9;12.7)	12.8 (12.4;13.2)	<0.0001
77.2 (75.9;78.5)	92.8 (92.1;93.5)	95.7 (95.1;96.3)	93.4 (93.0;93.8)	96.7 (96.5;96.9)	98.5 (98.4;98.7)	<0.0001
146.7 (146.0;147.4)	145.9 (145.3;146.5)	144.6 (144.0;145.2)	141.9 (141.7;142.2)	141.2 (140.9;141.4)	140.0 (139.8;140.2)	<0.0001
33.2 (31.5;34.8)	37.9 (36.4;39.3)	40.8 (39.3;42.2)	43.0 (42.2;43.7)	44.6 (43.9;45.2)	47.7 (47.1;48.3)	0.0003
46.7 (45.1;48.2)	69.7 (68.4;71.0)	72.7 (71.4;74.0)	73.5 (72.8;74.1)	73.7 (73.2;74.3)	74.6 (74.1;75.1)	<0.0001
77.2 (75.9;78.5)	79.5 (78.4;80.7)	87.8 (86.9;88.8)	83.1 (82.6;83.7)	84.2 (83.7;84.6)	94.2 (94.0;94.5)	<0.0001
4.0 (3.9;4.0)	3.8 (3.8;3.9)	3.8 (3.7;3.8)	3.6 (3.6;3.7)	3.7 (3.7;3.7)	3.8 (3.8;3.8)	<0.0001
55.0 (53.2;56.7)	59.2 (57.7;60.8)	61.7 (60.2;63.2)	67.1 (66.3;67.8)	64.5 (63.8;65.1)	61.1 (60.5;61.7)	<0.0001
21.7 (20.4;23.0)	35.8 (34.5;37.2)	40.1 (38.7;41.5)	54.3 (53.6;55.1)	59.7 (59.1;60.4)	62.8 (62.2;63.3)	<0.0001
84.7 (83.6;85.8)	85.7 (84.7;86.7)	93.1 (92.4;93.9)	87.8 (87.3;88.3)	85.5 (85.1;86.0)	95.4 (95.1;95.6)	<0.0001
95.4 (52.9;137.8)	96.5 (53.9;139.1)	97.7 (55.6;139.7)	92.9 (47.0;138.7)	98.9 (52.9;144.8)	98.7 (51.9;145.5)	<0.0001
57.4 (55.9;58.9)	62.0 (60.6;63.4)	69.9 (68.5;71.2)	59.0 (58.3;59.7)	66.8 (66.2;67.4)	82.3 (81.9;82.8)	<0.0001
22.1 (20.4;23.8)	24.4 (22.9;26.0)	23.2 (21.8;24.7)	19.2 (18.5;20.0)	19.8 (19.2;20.4)	18.5 (18.0;19.0)	<0.0001
3.7 (2.9;4.4)	3.9 (3.2;4.6)	4.2 (3.5;4.9)	2.9 (2.6;3.2)	2.5 (2.2;2.7)	2.4 (2.2;2.6)	<0.0001
62.3 (60.8;63.8)	83.0 (82.0;84.1)	88.4 (87.5;89.4)	78.1 (77.5;78.7)	88.1 (87.7;88.5)	93.1 (92.8;93.4)	<0.0001
29.6 (29.4;29.7)	29.6 (29.5;29.8)	29.5 (29.4;29.7)	29.5 (29.5;29.6)	29.5 (29.5;29.6)	29.5 (29.5;29.6)	0.1399
16.2 (14.8;17.7)	16.1 (14.9;17.2)	16.3 (15.1;17.4)	16.8 (16.2;17.4)	17.1 (16.6;17.6)	17.1 (16.6;17.6)	0.6638

Outcome measures

Figure 2 presents the trends for outcome measures over time for the overall study group and also stratified according to the 3 age categories.

Glycemic control and diabetes treatment

The decline in mean HbA1c over time is reflected in the proportion of patients achieving the target value of <7%; 35.8% in 1998 compared to 67.0% in 2008. The differences between the 3 age categories seem to be small, although the proportion of patients with an HbA1c ≥8.5% tended to be the highest for patients aged <60 years in all years (p for interaction with age 0.0773). The proportion of patients treated with only a diet increased over time from 16.6% to 23.8%. A total of 15.5% used insulin in 1998 and this proportion declined to 12.8% in 2008.

Blood pressure and treatment

Mean blood pressure has decreased over time in all age groups, with the lowest values in the youngest patient category (p for interaction with age <0.0001). In 1998 about one fifth (22.0%) had a systolic blood pressure <140 mmHg, compared to 47.7% in 2008. The number of patients with antihypertensive medication increased in all age groups. With advancing age the number of patients using these agents also increased (p for interaction with age <0.0001). A remarkable decrease in 2003 was directly followed by a large increase in 2004.

Lipids and treatment

Mean total cholesterol-HDL ratio has decreased in the period 1998-2006, followed by a small increase in the last two years (p for quadratic trend <0.0001). Patients aged <60 years performed worse with regard to the mean cholesterol-HDL ratio compared to the older patients categories (p for interaction with age <0.0001). Approximately one quarter (23.0%) of the patients participating in 1998 had a ratio <4. This proportion increased to 61.1% in 2008, which is also reflected in the number of patients receiving lipid-lowering drugs: 10.2% in 1998 and 62.8% in 2008. As was the case with the number of patients using antihypertensives, a remarkable decrease was also observed for the number of patients using lipid-lowering drugs in 2003.

Renal function

Mean values of serum creatinine have remained rather constant throughout the whole study period. The prevalence of micro- and macroalbuminuria in 1998 was 33.6% and 8.3%, respectively. These proportions declined over time to 18.5% and 2.4%, respectively. The highest prevalence of microalbuminuria was observed for the group >75 years (p for interaction with age <0.0001).

Body mass index

After an increase in the first five years, mean BMI remained rather constant afterwards. In the highest age category, the highest proportion of patients with a BMI <25 kg/m^2 was observed and vice versa (p for interaction with age <0.0001).

Discussion

Quality of diabetes care within the Dutch ZODIAC study, a shared care project, has considerably improved in the period 1998-2008. Large improvements were observed for all quality indicators studied in this study, except for BMI. Each time that large groups of general practices joined the shared care initiative (2002 and 2006), there was a short relapse in the process measures, which was mostly redressed within one year. No relevant differences between the trends for the 3 age categories were observed. During all years of follow-up, mean blood pressure and BMI were the lowest and highest, respectively, in the group of patients <60 years. Patients in this age category also had the highest cholesterol-HDL ratio values and the lowest albumin-creatinine ratio values throughout the whole study period.

Striking changes were the increase in the use of blood pressure and lipid lowering drugs. This increased use was also reflected in the improvements in blood pressure and lipid levels. Remarkably, the decrease in HbA1c was not accompanied by an increase in the proportional use of oral blood glucose lowering drugs or insulin. Instead, an increase in the proportion of patients on a diet was observed for all age categories. One could hypothesize that more patients with early diagnosed T2DM were included in the last years of the study. However, median diabetes duration did not relevantly change throughout the study. Patient education and better adherence to lifestyle advices could be other possible explanations.

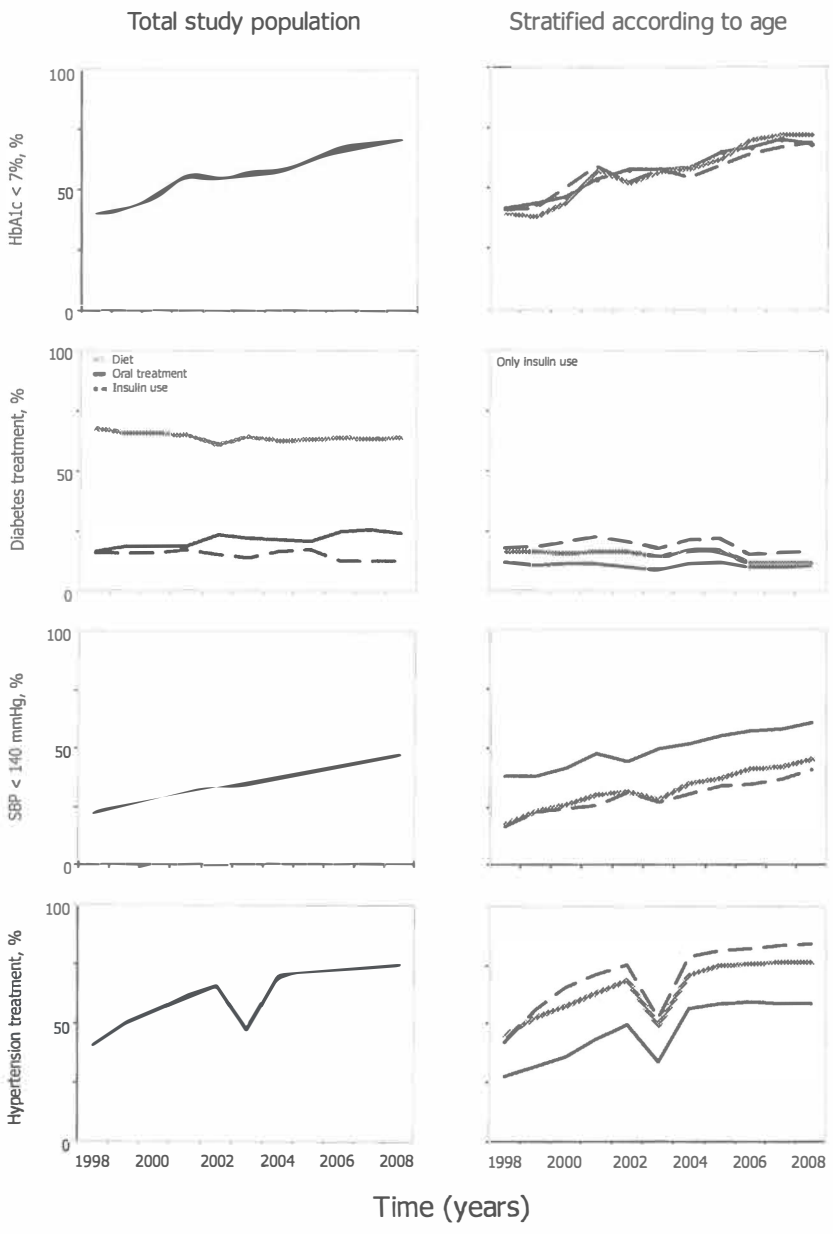
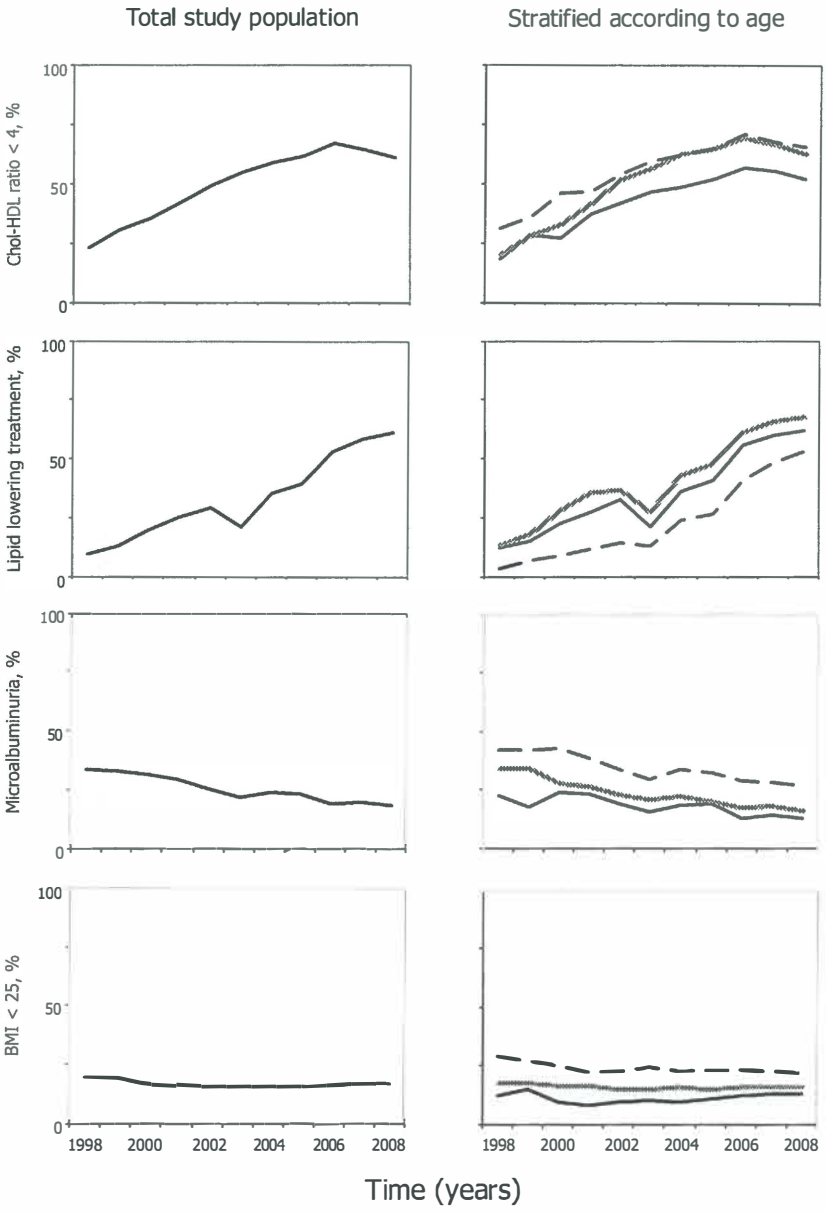


Figure 2. Outcome measures for the total study population and stratified according to age (<60 (black line), 60-75 (grey line) and >75 (black dashed line) years).


Total study population
Stratified according to age
Chol-HDL ratio < 4, %
Lipid lowering treatment, %
Microalbuminuria, %
BMI < 25, %
100
50
0
1998
2000
2002
2004
2006
2008
Time (years)

The results of our study confirm previous reports that also observed improvements in risk factor control during the past decades [9-11,22]. However, this is the first study presenting the results of a large shared care project with a follow-up period of more than 10 years. Although this study demonstrates the impressive results that have been achieved in a shared care setting, it should be emphasized that causality cannot be proved by our study. The two decreases in the process measures, that were observed after the expansion of the ZODIAC project in 2002 and 2006, and the quick rebound afterwards, suggest positive effects of participating in the project (figure 1). However, there are many other factors that may also explain the improvements in quality of care. Firstly, national and international guidelines advocating stricter treatment in patients with T2DM have been published in the period 1998-2008. For example, in 1999 and in 2006 revisions of the guideline T2DM of the Royal Dutch College of General Practitioners were published [18,23]. It could be that adherence to these guidelines, irrespective of participating in shared care projects, is the most important factor explaining the general tendency to improved diabetes care. Secondly, financial incentives from health insurance companies for general practitioners that provide care of a high quality have been introduced in the past decade. Although a recent Cochrane review concluded that there is insufficient evidence to support the use of such financial incentives, positive effects on quality of care can also not be excluded [24].

To our knowledge, our study is the first study that also specifically investigated the trends in diabetes care for patients aged older than 75 years. This population is of special interest for two reasons. Firstly, more than one quarter of the type 2 diabetic population in primary care in the Netherlands is >75 years. Secondly, clinical trials in old age investigating cardiovascular risk interventions, such as hypertension treatment, are either lacking or subject to selection bias [25-27]. Since the evidence for strict cardiovascular risk control in old age is low, old age is characterized by a high prevalence of complications and comorbidities, and elderly patients are at increased risk for possible adverse events, less strict treatment targets for elderly patients with T2DM have been advocated in literature [28-30]. Generally speaking, individualizing target values is more and more advocated in literature nowadays [30]. Take for example hypertension treatment in old age. Whereas a systolic blood pressure target value of 140 mmHg should be used for patients >75 years without many comorbidities who are not using insulin, it is unknown whether this target value is also appropriate for the overall elderly population [27]. In conclusion, although the current study observed the same improvements in the various quality measures across all age categories, it remains unsure whether these improvements will have the same beneficial effects on cardiovascular comorbidity and mortality in the oldest elderly as in younger patients with T2DM.

Our study has several important limitations that need to be addressed. Firstly, it is important to realise that the cross-sectional data presented in table 2 and figure 2 are influenced by changes in population (in- and outmigration), besides possible changes in quality of care. Since the estimated linear time trends were based on individual changes over time, it is possible to conclude that there is an improvement over time. However, these improvements are probably smaller than the cross-sectional data suggest, since cross-sectional outcomes on HbA1c overestimate improvements over time when compared to longitudinal outcomes [20]. Secondly, because of its observational design a causal relationship between shared care and the observed improvements cannot be proven. Unfortunately, we were not able to include a control group of patients with diabetes receiving standard care. Thirdly, the data in our study have been provided by practice nurses and GPs as part of the yearly benchmark. As a consequence, the quality and reliability of the data is dependent on the accuracy of the data providers. For example, the number of patients using lipid lowering treatment in 2003 is an extreme outlier compared to the other years and is probably not representative for the actual number of patients. This difference suggests a fault in providing or collecting the data. When a patient is registered as not using a statin, this could either mean that he or she is actually not using a statin or that it is incorrectly registered. However, with respect to the process parameters this may have led at the most to an underestimation of the actual measures. Also, our study only comprises patients whom data have been reported by the GPs. It is not unlikely that GPs have opted not to provide data of patients who never show up at their diabetes check-ups. Furthermore, the number of patients who did not participate in the study due to short life expectancy of insufficient cognitive abilities is unknown after 1999.

Strengths of our study are the long follow-up period and the high number of participants, especially in the last years of the ZODIAC study. Because of the size of our database, it is important to realize that small differences may easily lead to statistical significant differences while some can hardly be called relevant. For example, the mean serum creatinine level fluctuates around 95 µmol/L throughout the whole study period, but there is a slight positive (i.e. upward) linear trend for males above 75 years, while for women there is a slight negative linear trend for all age categories while the overall linear (very slightly positive) trend is nevertheless highly significant ($p<0.0001$).

In conclusion, our study shows that quality of diabetes care within the Dutch ZODIAC study has improved in the period 1998-2008, irrespective of age. Future studies are needed to elucidate whether there is a causal relationship between shared care and the improvements. Whether the large improvements observed in old age will lead to reductions in morbidity and mortality, remains also to be determined.

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Chapter 10

Time for considering new blood pressure target values in elderly patients with type 2 diabetes?

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Although blood pressure control has undoubtedly proven its benefits in reducing the high cardiovascular risk in patients with type 2 diabetes mellitus (T2DM), it still remains unclear whether intensive antihypertensive treatment in old age (>75 years) is beneficial. Many of the current guidelines recommend a systolic blood pressure (SBP) <140 mmHg or lower, unless patients are at high risk for possible adverse events such as postural hypotension [1,2]. This perspective aims to get a discussion started on the appropriate target SBP value for patients with T2DM aged older than 75 years. We would like to propose the less stringent value of <160 mmHg in this specific population.

There are two important arguments why we propose this new target value. Firstly, it is questionable whether the definition of hypertension should be the same for all age categories. Data from the Framingham study suggest that the threshold of SBP, at which it becomes related to increased mortality, increases with higher age [3]. For men aged 65-74 years the threshold lies around 160 mmHg, whereas the threshold for men aged 45-54 years lies around approximately 140 mmHg. When extrapolating these data, the threshold for patients aged older than 75 years may even be higher. Secondly, and even more important, the evidence for targeting a SBP <140 mmHg is essentially absent in older age. Although various studies investigated hypertension treatment in patients aged older than 60 years, no formal studies have been performed in the oldest elderly with T2DM. In this context, it is important to realize that more than one quarter of the primary care population with T2DM in the Netherlands is older than 75 years. Below, we will review the studies of old age and illustrate the selection bias which often occurs in these studies.

In the observational ZODIAC-12 and Botnia studies, an inverse relationship between mortality and blood pressure in elderly patients with T2DM was found [4,5]. Co-morbidities, frailty, side-effects of antihypertensive medication, and excessive lowering of blood pressure are all possible explanations of this relationship. Subanalyses of the SHEP study showed that certain decreases in diastolic blood pressure were related to increased cardiovascular events, possibly suggesting overtreatment in these patients [6]. In the general elderly population, an inverse relationship has been described many times before and was one of the main reasons to perform a randomised controlled trial in the oldest elderly from the general population: the HYVET study [7]. Unfortunately, there are no randomised controlled trials that have specifically investigated the effects of antihypertensive treatment in patients with T2DM >75 years. To our knowledge, there is only one study (ADVANCE) that performed a subanalysis for this specific age category [8]. Although the HYVET and ADVANCE studies were well-designed, we wish to argue that both studies were subject to selection bias. Generally speaking, elderly patients are underrepresented in clinical trials of cardiovascular disease [9,10]. Arbitrary age limits are used in many trials. Furthermore, the participation of elderly patients is also limited because of the

presence of exclusion criteria which strongly correlate with advancing age, including common medical conditions and commonly prescribed drugs [10]. In our opinion, the possibility of selection bias should be considered more often when translating the results of clinical trials into recommendation for elderly patients.

The HYVET study showed that in patients over the age of 80 without heart failure for whom antihypertensive therapy was considered indicated, a reduction in blood pressure resulted in improved cardiovascular morbidity as well as cardiovascular and all-cause mortality [7]. The target SBP value was 150 mmHg, which was achieved in 48% of the patients in the active treatment group after two years of treatment. The baseline SBP was 173 mmHg in both the active treatment and placebo groups. After two years, the between-group difference in the reduction of SBP was 15.0 mmHg: mean SBP had fallen 29.5 mmHg and 14.5 mmHg in the active treatment and placebo groups, respectively. The baseline characteristics show that only relatively healthy patients were included. The proportions of patients with a history of cardiovascular disease (12%) and diabetes (7%) were very low. This diabetes prevalence is remarkably low compared to the known prevalence of approximately 15% in elderly U.S. patients aged ≥ 75 years [11]. Unfortunately, no separate analysis of the diabetes group has been published up to now.

In the ADVANCE study, positive effects were observed for adding a fixed combination of perindopril and indapamide to the already prescribed antihypertensive drugs in patients with T2DM [8]. Patients were included when they were aged 55 years and older, and were required to have at least one additional risk factor for cardiovascular disease besides T2DM. Patients with a definite indication for long-term insulin therapy were excluded. There were no blood pressure criteria for inclusion. Subanalyses of this study showed that clinical benefits were also observed in patients of at least 75 years [12]. Active treatment compared with placebo reduced SBP by 6.9 mmHg in this age category (baseline SBP was 145 mmHg). The hazard for cardiovascular mortality in the active treatment group was 35% lower compared to the placebo group (Hazard ratio (HR) 0.65 (95%CI 0.44-0.98)). No significant relationship was observed for all-cause mortality (HR 0.90 (95%CI 0.68-1.19)). The authors concluded that the greater absolute benefits in older patients were not offset by an increased risk of side effects.

We would like to consider some arguments to support our hypothesis that the population of the ADVANCE study was also subject to a certain degree of selection bias. For this purpose, we compared the elderly cohort of the ADVANCE study (≥75 years) with the elderly patients in our observational ZODIAC study, in which we observed the inverse relationship between blood pressure and mortality in elderly diabetic patients [3]. The ZODIAC study is an observational study of patients with T2DM who are treated exclusively in primary care [13]. Data on mortality

are known for the patients who were included in 1998 and the beginning of 1999. Patients with a very short life expectancy (including patients with active cancer) or insufficient cognitive abilities were excluded (~5%). Nearly 90% (n=1357) of the remaining patients agreed to participate. For this perspective, we selected all patients aged ≥75 and ≤81 years, not using insulin, in order to select a cohort of patients comparable to the ADVANCE cohort with respect to age and insulin use (n=227). Table 1 presents the baseline characteristics of both study populations. Median age (interquartile range) in both cohorts was 77 years (76-79). The ZODIAC population comprised more female patients, had a higher mean SBP, and a higher median albumin-creatinine ratio. These baseline differences are also reflected in the all-cause mortality rates of both studies. Figure 1 shows the mortality rates of the elderly cohorts of the ZODIAC and ADVANCE study, including the estimated mortality rate for the age-matched general population in the Netherlands in 2000 (http://statline.cbs.nl/StatWeb/). After a follow-up period of approximately 5 years, 19% of the study population (192 out of 1008) had died in the ADVANCE study, compared to 35% in the ZODIAC cohort. Remarkably, the elderly diabetic patients in the ADVANCE study had a better life expectancy than patients from the general population of the Netherlands.

	ADVANCE *n=1008*	**ZODIAC *** *n=227*
Age (years)	77 (76-79)	77 (76-79)
Female	403 (40%)	151 (67%)
Macrovascular complications	370 (37%)	101 (45%)
Currents smokers	60 (6%)	21 (9%)
Systolic blood pressure (mmHg)	151 (22)	158 (24)
Body-mass index (kg/m²)	27.8 (4.6)	27.7 (4.5)
Serum creatinine (µmol/L)	91 (80-107)	95 (82-111)
HbA1c (%)	7.3 (1.4)	7.3 (1.2)
Total cholesterol (mmol/L)	5.0 (1.1)	5.7 (1.2)
Albumin-creatinine ratio (µg/mg)	16.8 (7.5-45.1)	30.5 (13.1-81.0)

Table 1. Baseline characteristics of the ADVANCE and ZODIAC cohorts. Patients not using insulin and those aged >81 years were excluded from the ZODIAC cohort in order to select a cohort of patients more comparable to the ADVANCE cohort.

It is interesting to generate hypotheses on the difference in mortality rate between the two studies. Firstly, the difference in mortality rate may be due to a treatment effect. However, the total mortality rate in the placebo arm of the ADVANCE study was also only 20%. Since the ADVANCE study started three years after the ZODIAC study was initiated, the characteristics of the ZODIAC participants in 2001 may be quite different from the 1998 participants. Indeed, the mean SBP of patients aged ≥75 years was 156 mmHg in 1998 compared to 149 mmHg in 2001. Finally, we can not exclude the possibility that differences in treatment of other cardiovascular

risk factors during the follow-up period of both studies may have contributed to the difference in mortality. However, it is not likely that such differences may be responsible for an absolute difference of 15% in mortality. In our opinion, these data suggest that elderly patients included in the ADVANCE study do not represent the general diabetic population.

We acknowledge that it is quite difficult to translate the results of the available studies into guidelines that can be used for daily practice, especially given the heterogeneous health status of elderly patients. Nevertheless, we would like to propose a SBP target value of 160 mmHg in this patient category. Based on the ADVANCE subanalysis, a target value of 140 mm Hg should be considered for healthy patients with T2DM who are not treated with insulin. For all other patients a target value of 160 mm Hg may be more appropriate.

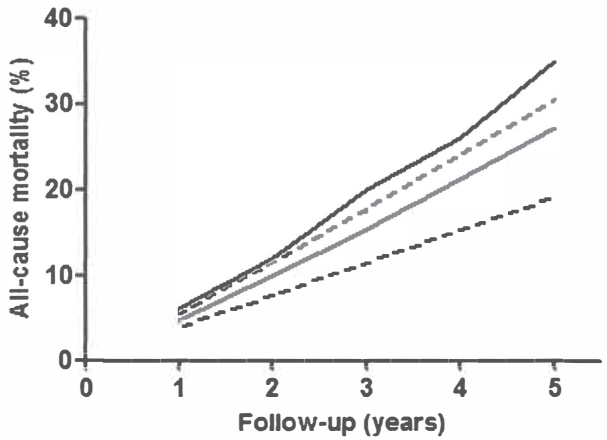

Figure 1. All-cause mortality rates of the ADVANCE and ZODIAC cohorts, and the age-matched general population in the Netherlands. The black line indicates the mortality rate in the ZODIAC study. The black dashed line is the estimated survival curve for the elderly patients in the ADVANCE study, based on the mortality rate at the end of the study (19%). The gray lines are the estimated mortality rates for the general population aged 77 years in the Netherlands in 2000. Since we only had the sex-specific mortality rates we calculated the overall mortality rate based on the male-female ratio in the ADVANCE (gray dashed line) and ZODIAC (gray line) cohorts.

We would like to emphasize that we are not recommending against the initiation of antihypertensive treatment in elderly T2DM patients. However, in order to make valid recommendations concerning treatment and treatment targets in hypertension at an older age, a pragmatic randomised controlled trial will be necessary, targeting this specific patient population. Until a higher level of evidence is reached, we recommend a relaxation of the guidelines with respect to the target blood pressure level in the general elderly diabetic population. Where the current guidelines advocate treatment unless there is a risk of adverse events, we propose the opposite: a less stringent standard target value unless there are arguments for strict treatment.

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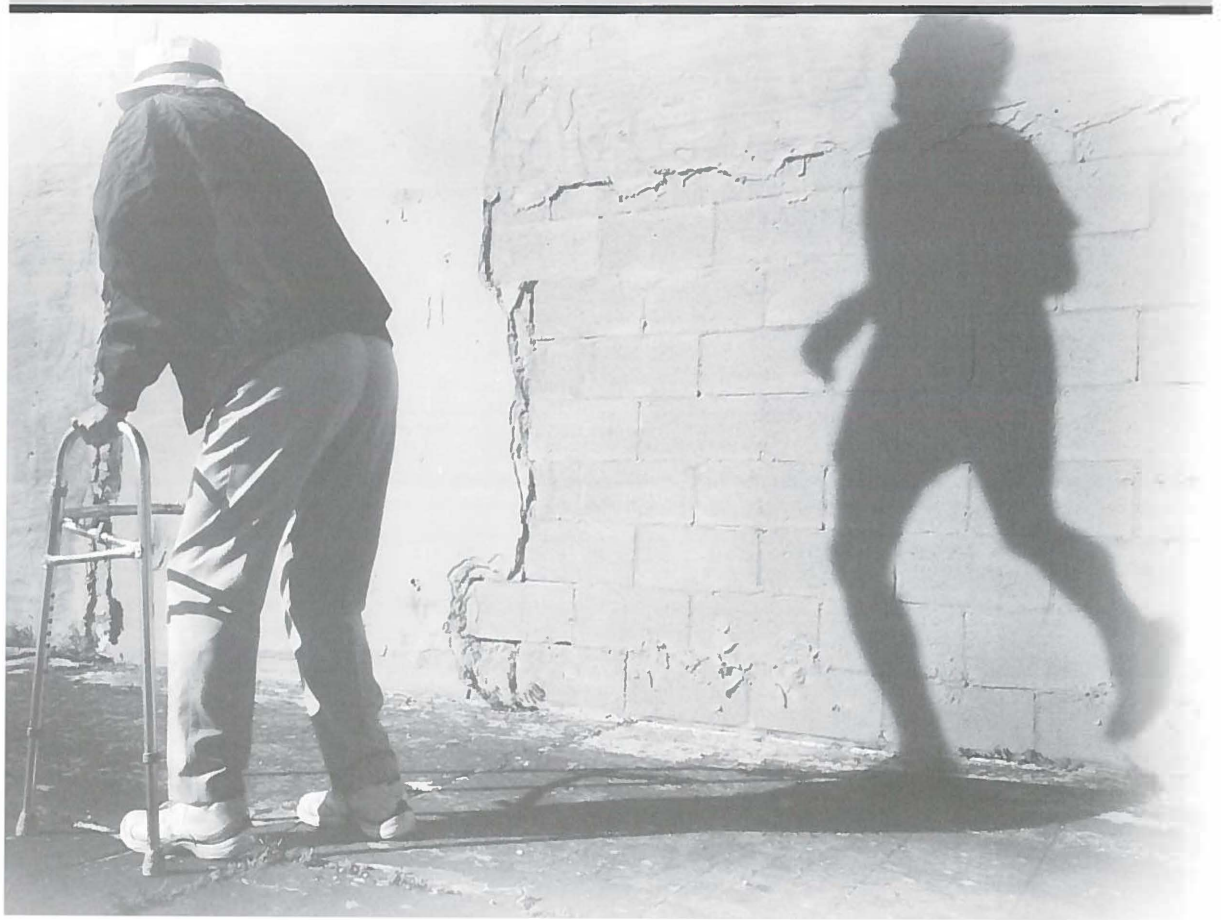
Chapter 11

Discussion



This thesis showed that important cardiovascular risk factors have different clinical consequences in elderly patients with type 2 diabetes mellitus (T2DM). Together with the underrepresentation of elderly patients in clinical trials and the selection bias that occurs in trials with patients of old age, it can be concluded that there is no evidence supporting the presently widely accepted idea to use the same therapeutic strategies for elderly patients as we use for the 'general' patient with T2DM.

I would like to emphasize the 'take home message' of this thesis at the beginning of this chapter: health care providers should loosen the reins on treatment goals of elderly patients with T2DM, unless there are clear arguments for strict treatment. This view conflicts with current guidelines, but does fit the principles of evidence-based medicine much better.

Main results and implications for daily practice

In this section the possible implications of this thesis will be discussed and the results will be compared with current literature.

Cardiovascular risk management

The decreasing life expectancy with advancing age and the phenomenon of competing risks, as discussed in the introduction of this dissertation, are important characteristics of the elderly population. A diagnosis of T2DM late in life will have less impact on life expectancy and risk of diabetes-related complications than a diagnosis early in life. A similar phenomenon is observed when evaluating the effectiveness of therapeutic strategies in old age. On the one hand, the absolute risk of cardiovascular events in old age is high, and as a consequence only few patients have to be treated to prevent one event. In other words, the Number Needed to Treat (NNT) to prevent a cardiovascular event is low. On the other hand, the gain in life expectancy and event-free life expectancy declines with advancing age. Therefore, the use of solely absolute risks, i.e. the NNT, to justify preventive strategies does not seem to tell the whole story in aged populations [1]. Unfortunately, the majority of cardiovascular disease studies does not present data on the gain in (event-free) life expectancy. In the paragraphs below, I will discuss clinical trials in old age; NNTs will be provided or calculated where possible.

Glycemic control

The results presented in **Chapter 2,** showed that poor glycemic control is related to increased all-cause and cardiovascular mortality in elderly patients, but only in those with diabetes of short duration (<5 years). This prospective observational study was the first study in which the relationship between HbA1c and mortality in patients >75 years was investigated. A few months later a retrospective cohort study by Huang et al. was published in which age-specific

analyses were performed for the association between glycemic control and mortality [2]. This association weakened with advancing age. For patients aged 80 years and older (n=10.395), a HbA1c level between 42 mmol/mol and 64 mmol/mol was related to decreased mortality when compared to lower HbA1c levels. The authors mention in the discussion that they did not find statistically different results with differing durations of diabetes [2]. Unfortunately, these data were not presented.

The results of our observational study correspond with previous randomised controlled trials that showed that, with respect to mortality, intensive glucose control may only be beneficial in those with diabetes of short duration [3-6]. Nowadays, individualizing glycemic target values is more and more advocated in literature [7-10], and diabetes duration seems to be an important factor to consider. Over a period of 10 years, intensive glucose-lowering therapy led to a reduced microvascular risk, but not a reduced macrovascular risk, in the overall population of the UKPDS study [12]. The post-trial monitoring study was initiated to study whether improved glycemic control, achieved during the interventional period, would also lead to a continued vascular benefit on the long term. Despite an early loss of glycemic differences between the study groups, positive effects on the incidence of microvascular risk and also myocardial infarction were observed during 10 years of post-trial follow-up [11]. These data are another argument for putting most efforts in optimizing glycemic control in patients with recently diagnosed diabetes. Based on our study, one may suggest that this also holds true for elderly patients. However, it is important to emphasize that, in general, less intensive target values should be used in the elderly population. Besides the lack of randomised controlled trials, there are other arguments for less strict treatment in old age.

Firstly, it takes years to develop diabetes-related complications. In the UKPDS study, it took 6 to 9 years before a difference in the incidence of microvascular complications between strict and less strict control was observed [12]. This study did not show beneficial effects on macrovascular complications, except for overweight patients who were primarily treated with metformin [13]. For these patients, a reduction in macrovascular complications was observed 6 to 9 years after study initiation. However, based on the results of the overall UKPDS study population, it probably takes 10-20 years to develop macrovascular complications for the 'average' patient with newly diagnosed diabetes [11]. Optimizing glycemic control in elderly patients with recently diagnosed diabetes, in order to reduce complications, seems only justified in those patients with an estimated life expectancy of more than five years. On the other hand, symptoms of hyperglycemia and signs of microvascular complications, such as microalbuminuria and beginning retinopathy, can also be arguments for optimizing glycemic control.

Secondly, the risk of hypoglycemic episodes in old age is another important issue that should be addressed. The 2003 guideline by the American Geriatrics Society stated that a target value of 64 mmol/mol would be appropriate for frail elderly patients [14]. The implications of this guideline were investigated in a study amongst patients who were unable to live independently [15]. The proportion of patients with an HbA1c ≥ 64 mmol/mol decreased from 26% to 16%. Although implementation of this guideline resulted in less hyperglycemic episodes, the rate of severe hypoglycemic episodes requiring emergency department visits increased in the early implementation period, rising from 1.1 to 2.9 episodes per 100 persons-years [15]. These data indicate that even a target value of 64 mmol/mol, which is well above the target values used in the general diabetic guidelines, leads to important adverse effects in very frail elderly patients.

Finally, the NNT for glucose-lowering treatment in the general diabetic population showed that it would be necessary to treat 140 patients with intensified glycemic control for 5 years in order to prevent one case of coronary heart disease. The NNTs to prevent one person developing blindness or renal failure were 272 and 627, respectively [16]. These numbers are based on a meta-analysis, in which more intensive treatment led to a mean HbA1c reduction of 10 mmol/mol compared to the less intensive treatment group [17]. Since there are no randomised controlled trials or subanalyses of trials that have specifically investigated the effects of glucose-lowering treatment in old age, NNTs for this age category cannot be presented.

Individualising target values for glycemic control is important because the balance between positive and negative effects of glucose-lowering treatment is very delicate in old age. Several factors, including estimated life expectancy, the degree of frailty and diabetes duration, determine the optimal target value at which the positive and negative effects are counter-balanced. However, it is not easy to estimate someone's remaining life expectancy and the level of frailty. I will put forward some thoughts on this matter further on in this chapter. The guideline of the 'Dutch Association of Elderly Care Physicians and Social Geriatricians' recommends that a target value of 69 mmol/mol is acceptable for elderly frail patients with an estimated life expectancy of less than 5 years [18]. In my opinion, a standard target value of 64 mmol/mol seems to be appropriate for the majority of patients aged older than 75 years. Our study suggests that more intensive treatment may be beneficial in healthy elderly patients with recently diagnosed T2DM. Even higher values should be considered for patients with many co-morbidities, a reduced life expectancy and a high level of frailty. Preventing hypoglycemic episodes and hyperglycemic symptoms should be the most important aim for these patients.

Lipids

The results in **Chapter 3** showed that for patients aged 60-75 years, higher levels of LDL cholesterol were related to increased all-cause and cardiovascular mortality. No associations between lipids and mortality in the overall group of elderly patients (>75 years) were observed. However, the results were different when stratified for diabetes duration. In elderly patients (>75 years) with a diabetes duration of 8 years or more, higher LDL levels were related to increased cardiovascular mortality. These results seem to confirm that patients with short-duration and long-duration diabetes represent distinct groups with differing burdens of disease [19]. However, it is important to realise that the analyses were stratified according to diabetes duration within different age groups. As a result, the groups became small and the results should be interpreted with caution.

The question whether we should prescribe statins for elderly patients with diabetes is an important dilemma in daily practice. The guideline of the 'Dutch Association of Elderly Care Physicians and Social Geriatricians' recommends to prescribe all elderly patients with diabetes a statin unless the estimated life expectancy is ≤ 2 years [18]. However, I would like to question this recommendation. There are several arguments supporting a more conservative approach, which is also more evidence-based. Firstly, it is important to realise that the role of lipids as a cardiovascular risk factor declines with advancing age. It is correct that for patients in the general population higher cholesterol is related to increased mortality from ischaemic heart disease (IHD), even for persons aged over 80 years [20]. However, this relationship became substantially attenuated with higher age and no positive association was found between cholesterol and stroke mortality [20]. For elderly patients with T2DM the evidence is limited to our observational study, and we found no association with mortality in the overall group of elderly patients.

Secondly, diabetic patients aged >75 years are also underrepresented in clinical trials. As a consequence, the evidence for prescribing lipid-lowering treatment in the oldest elderly is very limited. A large meta-analysis, in which more than 18.000 patients with diabetes from 14 randomised controlled trials of statins were included, has performed separate analyses for patients aged 65 years and older [21]. These analyses showed beneficial effects of lipid-lowering treatment on major vascular events. However, the majority of these patients were younger than 75 years of age because only 5 out of the 14 trials had included patients >75 years. The PROSPER study was specifically designed to study the effects of cholesterol-lowering treatment in patients aged 70-82 years with either pre-existing vascular disease or an increased cardiovascular risk because of smoking, hypertension or diabetes [16]. Only 623 out of the 5804 patients included in this study had diabetes. The hazard ratio of pravastatin for cardiovascular events, compared to the placebo group, for patients with and without diabetes

were 1.27 (95% confidence interval (CI): 0.90-1.80) and 0.79 (95% CI: 0.69-0.91), respectively [22]. In other words, patients without diabetes who received pravastatin had a 21% lower risk of developing a cardiovascular event compared to patients in the control group. Although the number of patients with diabetes was probably too small to permit an accurate interpretation of the treatment effect, the interaction between the diabetes and treatment groups was statistically significant. This suggested that patients with diabetes, aged 70-82 years, did worse than those without diabetes [23]. Based on the event rate in the overall PROSPER study population, the NNT for 5 years of lipid-lowering treatment to prevent 1 cardiovascular event was 30, while treatment had no beneficial effects on all-cause mortality [22].

Thirdly, selection bias makes it more difficult to translate the results of a clinical trial into recommendations for daily practice. Since the baseline characteristics of diabetic patients included in the PROSPER study have not been published, it is not possible to compare those patients to the diabetic patients in the ZODIAC study. In the overall PROSPER population 48% was male, yet one would expect a lower male-female ratio at a higher age. In 1999, the first year of the PROSPER study, approximately 60% of all inhabitants in the Netherlands aged 70-80 years was female. For the age category 80-90 years this proportion was even almost 70% (http://statline.cbs.nl/StatWeb/). These data suggest that at least a certain amount of selection bias occurred in the PROSPER study.

Finally, the possibility of side effects are an important factor to considerwhen prescribing statins. Although the PROSPER study did not observe an increased incidence of reported myalgias, rhabdomyolysis or decline in cognitive function [22], it should be questioned whether these results also apply for elderly patients in daily practice. Generally speaking, these patients have a higher level of frailty than patients included in clinical trials, and therefore it is not unlikely that they are more prone to side effects of statins. Statin-related myalgia is very common and its incidence varies between 5-18% in different studies [24,25]. For elderly patients who have already lost muscle strength and function, any further muscle complaints may lead to a further decline in physical functioning. Even in a cohort of generally healthy patients (no history of diabetes or cardiovascular disease) statin use was associated with fatigue and exertional fatigue [26]. Decline in cognitive function is another adverse event that is associated with statin use. Although the negative effects of statin use on cognitive function were quite modest in two trials that were specifically designed to investigate the cognitive effects of statins, these effects were observed in young adults with a mean age of approximately 50 years [27,28]. For elderly patients, of which a majority will already have experienced loss of cognitive function, any modest effects may have more profound consequences in daily practice.

Based on the aforementioned arguments, a conservative approach seems justified when prescribing statins, especially with respect to primary prevention. However, this does not imply that we should stop prescribing statins to elderly patients. Statins may be beneficial as a secondary prevention measure for elderly patients, but even for these patients one may choose not to prescribe statins because of frailty and limited life expectancy. For patients who are already on cholesterol-lowering treatment, continuing treatment seems the most pragmatic advice, except when patients experience side-effects.

Blood pressure

The results presented in **Chapter 4** showed that blood pressure is inversely related to all-cause and cardiovascular mortality in old age. In other words, higher blood pressure is associated with less mortality. For patients aged 60-75 years no relationship between blood pressure and mortality was found. Because of the possibility that heart failure may explain the inverse relationship between blood pressure and mortality through reverse causality, additional analyses were performed as presented in **Chapter 5**. Adjustment for the midregional pro-A-type natriuretic peptide (MR-proANP), as a surrogate variable for heart failure, did not change the inverse relationship between blood pressure and mortality at all. Although these analyses have made it less plausible that heart failure is the explaining factor for the inverse relationship, co-morbidities and frailty may still account for the inverse relationship, even though we tried to adjust for such aspects.

Although hypertension treatment in patients aged 80 years and older from the general population reduces the risk of cardiovascular events and heart failure, the effects on mortality remain unclear [29-32]. According to the results of the HYVET study, a study amongst patients >80 years of age without heart failure, 94 patients had to be treated for 2 years to prevent one stroke, and 40 patients to prevent one death [33]. The risk of all-cause mortality was 21% lower in the treatment group compared to the placebo group. Because of the unexpected beneficial effects, this study was prematurely interrupted. After the complete follow-up period, the risk reduction of all-cause mortality was still 21%, but the results were no longer significant when measured against the a-priori decided threshold of $p < 0.01$ [32]. It could be that the initial results were an overestimation, as is more often observed in trials that are prematurely analysed or terminated [34]. In an open-label randomised study amongst patients aged 65-85 years from the general population, the effects of strict antihypertensive treatment (SBP target value <140 mmHg) were compared with mild treatment (SBP target value <160 mmHg) [35]. The primary endpoint was defined as the combined incidence of cerebrovascular disease, cardiac disease and renal failure. Although there were no differences between both groups with regard to the primary endpoint, the authors did observe an interaction between age and treatment group. For patients aged 75 years and older the hazard ratio for the incidence of the

primary endpoint was below 1 (95% CI 0.50-1.11), while for younger patients the hazard ratio was above 1 (95% CI 0.92-2.34).

In the ADVANCE study, the effects of adding a fixed combination of perindopril and indapamide to the already prescribed antihypertensive drugs were investigated in patients with T2DM [36]. Patients were required to have at least one additional risk factor for cardiovascular disease besides T2DM, and patients using insulin or patients with a definite indication for long-term insulin therapy were excluded. The ADVANCE study is the only randomised trial that has performed subanalyses for patients aged ≥75 years. These analyses showed that treatment led to beneficial effects on cardiovascular mortality, but not all-cause mortality, in this specific age category [37]. Active treatment compared with placebo reduced SBP by 6.9 mmHg in this age category; baseline SBP was 151 mmHg and achieved SBP was 137 mmHg in the active treatment group. The NNT showed that 22 patients would have to be treated for 5 years to prevent one cardiovascular death [37].

Based on the above-mentioned results one could argue that there is a reasonable amount of evidence supporting antihypertensive treatment, even in elderly patients with T2DM. However, are the results of the ADVANCE study also applicable to the elderly diabetic population? In the perspective, presented in **Chapter 10**, it was showed that patients in the ADVANCE study are not representative of the 'average' elderly patient with T2DM. After a follow-up period of approximately 5 years, 19% of the study population (192 out of 1008) had died in the ADVANCE study, compared to 35% in our ZODIAC cohort. Remarkably, the elderly diabetic patients in the ADVANCE study even had a better life expectancy than patients from the general population in the Netherlands. Besides the selection bias of the ADVANCE study and lack of trials in old age, there are other arguments why less stringent values should be applied for elderly patients. Firstly, observational data do not confirm that hypertension is a risk factor in old age. Our study even showed an inverse relationship between blood pressure and mortality. Secondly, antihypertensive treatment may lead to adverse events, such as orthostatic hypotension (OH). Subanalysis of the meta-analysis by Bejan-Angoulvant et al., amongst hypertensive patients aged 80 years and older, indicated that the risk of mortality increased with more intensive therapy [30].

The increased risk of falling that is associated with OH is another argument for less intensive hypertension treatment in old age. A recent study showed that patients with OH have an increased risk of death due to injury [38]. The cross-sectional study in **Chapter 8** confirmed the presumption that OH is highly prevalent in home-dwelling elderly type 2 diabetic patients. Although no association was found between falling and OH, orthostatic complaints were associated with previous falling and high fall risk, even after adjustment for OH. Since falling

may lead to potential devastating injuries, it is important to recognize those patients with an increased risk of falling. Actively inquiring for orthostatic complaints is rather simple and may even be a more useful step than measuring OH.

In **Chapter 8** several limitations of our cross-sectional study were discussed. However, only little attention was paid to the definition of OH that was used in our study. Since we observed no relationship between OH and falling, and OH was not correlated to orthostatic complaints, our definition of OH can be a cause for debate. Analogous to the international guidelines, we defined OH as a fall in blood pressure of at least 20 mmHg systolic or 10 mmHg diastolic, after either one or three minutes of standing after the subject changed from the supine to the upright position [39,40]. This definition is based on an absolute decrease in either systolic or diastolic blood pressure. However, a decrease of 20 mmHg in systolic blood pressure may have different consequences for a subject with a sitting blood pressure of 180 mmHg than for a subject with a sitting blood pressure of 90 mmHg. Also, in a chronically hypertensive patient, cerebral autoregulation is often impaired, and such patients are more susceptible to orthostatic complaints with smaller drops in blood pressure [41]. Other aspects of the definition of OH are the time thresholds at which the standing measurements are performed, and whether the measurements can be reproduced. In my opinion, the definition of OH should be based on its associations with adverse health outcomes such as cardiovascular disease, mortality and falls. Therefore, prospective studies evaluating the prognostic properties of several definitions of OH are needed.

Since the relationship between OH, hypertension and antihypertensive treatment is rather complex, there is no clear-cut answer to the question what action should be taken after having identified an individual with OH or orthostatic complaints. On the one hand, antihypertensive agents may provoke or aggravate existing OH. A prospective study showed that withdrawal of cardiovascular drugs led to a reduction in OH incidence [42]. On the other hand, hypertension is an important cause of OH and therefore one may argue that appropriate hypertension treatment seems to be justified [43]. Also, in an observational cohort of nursing home patients, aged 80 years and over, OH was less prevalent among hypertensive patients with good control of their blood pressure (systolic blood pressure <140 mmHg) [44]. However, there are no trials that showed beneficial effects of hypertension treatment on OH. Therefore, it seems reasonable to detensify antihypertensive treatment in patients with orthostatic complaints and/or OH. For hypertensive patients with orthostatic complaints and/or OH, who are not using antihypertensive drugs, one may consider to treat hypertension first.

In conclusion, I suggest that a systolic blood pressure target value of 160 mmHg is suitable for the majority of elderly patients (>75 years) with T2DM. This target value is also recommended in the guideline of the 'Dutch Association of Elderly Care Physicians and Social Geriatricians'

[18]. For non-frail patients who are not treated with insulin, a target value of 140 mmHg is justified. For more frail patients with a limited estimated life expectancy even a higher target value than 160 mmHg can be considered. Furthermore, clinicians should pay attention to the presence of orthostatic complaints.

Moderately decreased renal function: pathological or not?

The significance of moderate reductions of the estimated glomerular filtration rate (eGFR) with advancing age is still debated. Some argue that an age-related decrease in eGFR should be considered as a physiological phenomenon, whereas others argue that the reduction of eGFR in elderly patients may reflect the high prevalence of kidney disease risk factors at a higher age [45]. In **Chapter 6** it was showed that, as opposed to type 2 diabetic patients aged 65-75 years, an eGFR (ml/min/1.73m^2) of 45-60 was not related to increased all-cause and cardiovascular mortality in the oldest elderly. The observed attenuation of the association of mortality with certain eGFR stages in older patients, was not found for albuminuria. For patients aged 65-75 years, as well as for patients >75 years, albuminuria was an independent marker of mortality.

Our results confirm the results from previous studies which showed that the association between eGFR and mortality risk attenuates with advancing age [46-49]. In one of these previous studies, a large meta-analysis amongst patients >65 years who had an increased risk of chronic kidney disease, albuminuria was also an independent marker of mortality [49]. Furthermore, an eGFR between 45 and 60 was only related to increased mortality in patients with albuminuria. Although this meta-analysis clearly showed that lower eGFR levels are associated with lower risks in old age, the authors of this meta-analysis concluded that their data did not provide evidence for using age-specific eGFR thresholds to define chronic kidney disease. They argued that absolute risk is higher in older patients and that the relative risks for cardiovascular mortality were more similar in older versus younger subjects, as opposed to the relative risks for all-cause mortality [49].

Amongst patients >75 years from the general population, the prevalences of an eGFR <60 and <45 were 56.1% and 17.7%, respectively. Having an eGFR <45 was associated with significant comorbidity, impaired functional state and a high risk of potentially reversible consequences such as anemia [50]. The absence of an association between an eGFR 45-60 and mortality, and the very high prevalence of an eGFR <60 at older age, underline the importance of considering an eGFR 45-60 as physiological at first. Based on other arguments, such as the presence of (macro)albuminuria or a rapid decrease in eGFR over time, it can be concluded that an eGFR between 45 and 60 may still be pathological for that specific patient. Finally, it is important to realise that we work with estimations of renal function in daily practice. The Modification of Diet in Renal Disease (MDRD) equation, that was used in our study, is an estimation of renal function and does not necessarily reflect the true value of renal function. Especially since the

MDRD was developed in a population younger than 70 years, this equation may be less useful in selecting elderly patients with true chronic kidney disease.

An eGFR 45-60 should be considered as physiological at first because it is not associated with increased mortality in old age. Albuminuria, on the other hand, remains an important and independent marker of mortality, irrespective of age. The Dutch national transmural agreement (LTA) for 'Chronic renal impairment' already promotes the use of age-related cut-off values for renal function. Using these cut-off values will result in more targeted referral to secondary care, especially for the elderly [51].

MR-proANP: useful for risk prediction?

Several risk engines are used for clinical decision making in daily practice [52-55]. Take for example the Systematic Coronary Risk Evaluation (SCORE), which use is advocated in the Dutch Guideline 'Cardiovascular risk management' [52,56]. Other examples are the Framingham risk calculation and the 'Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe' (DECODE) [53,54]. A review showed that these risk equations do not provide a reliable risk estimate of death in patients with T2DM, as compared with the UKPDS equation, which has specifically been designed for patients with T2DM [57]. However, even the UKPDS risk engine is only moderately effective in identifying those patients that are at high risk [57,58]. Our study group showed that the UKPDS equation overestimated cardiovascular disease mortality risk in Dutch patients with T2DM [59]. The predicted UKPDS fatal coronary heart disease event rate was 28.9% compared to an observed fatal cardiovascular disease rate of 17.6% in the ZODIAC study.

Although all risk engines include age as an important predictor of mortality, only the ZODIAC study included patients aged over 75 years [52-55,59]. Since this thesis, and a previous one in the general population, showed that the value of traditional cardiovascular risk factors appears to diminish with advancing age, other factors may become more important in old age [60]. In **Chapter 5** we showed that MR-proANP was an independent predictor of (cardiovascular) mortality. Adding MR-proANP to the models with all conventional risk factors resulted in small increases in the C values. Based on the small improvements in Harrell's C values when adding MR-proANP to the adjusted models, one may conclude that the additional value of MR-proANP in risk prediction seems rather limited. However, it is important to realise that it is difficult to achieve further improvements in risk prediction by adding a biomarker to models which already include all conventional risk factors [61]. In the present study, the C values of the fully adjusted models without MR-proANP in the overall population were 0.79 and 0.80 for all-cause and cardiovascular mortality, respectively. Such values leave little room for further improvements in risk prediction. The lowest C values were observed in the group of elderly patients, indicating that the prognostic properties of MR-proANP diminish with advancing age.

These results confirm that the effect of certain risk factors declines with advancing age. Other risk factors, of which (biological) age is the most important one, will be a greater determinant of someone's remaining life expectancy: the phenomenon of competing risks [62].

Based on our study, no definite conclusion can be drawn on the practical implications of MR-proANP for daily practice. One the one hand, it seems that the value of MR-proANP is limited with respect to predicting mortality. On the other hand, MR-proANP was independently associated with mortality in old age in contrast to some traditional risk factors. Therefore, future studies are needed to investigate what would be the most reliable risk equation for elderly patients with T2DM.

Quality of life

As argued in the introduction of this thesis, goals in diabetes management may be different for older patients with diabetes, or at least for a selected part of the elderly diabetic population. Improving or maintaining quality of life may be more relevant for a specific patient than aiming to reduce risk of complications and their associated mortality. In this context, it is interesting that HRQOL is an independent predictor of all-cause and cardiovascular mortality in these patients (**Chapter 7**).

In our study, HRQOL was measured using the RAND-36 questionnaire, which consists of 36 questions covering 9 aspects of health status. These 9 aspects can be divided into two component summaries: a Physical Component Summary (PCS) and a Mental Component Summary (MCS). These two summaries can be regarded as a marker of physical disabilities and depressive complaints, respectively, which would also explain the observed relationships with mortality. In other words, the relationship between the PCS and mortality is probably caused by physical disabilities. Although we adjusted for macrovascular complications in our multivariate analyses, it is not possible to adjust for all comorbidities and the level of frailty (residual confounding). A prospective study on frailty and pre-frailty, as defined with using the RAND-36 questionnaire, showed independent associations with mortality, walking speed and disability after 7 years of follow-up [63]. Non-frail patients had a better survival, walked faster and had less disabilities. These relationships confirm the hypothesis that comorbidity and frailty explain the relationship between the PCS of the RAND-36 and mortality. Therefore, we should probably have used the RAND-36 questionnaire to adjust for frailty, instead of excluding the first years of follow-up like we did in several chapters of this thesis.

The relationship between the MCS and mortality can be regarded as a confirmation of the increased mortality risk that is associated with depression [64]. Several explanations have been proposed for the increased mortality risk in depression, including increased suicide rates, a

higher prevalence of unhealthy life style factors and the presence of comorbid conditions such as diabetes or cardiovascular disease [65]. Assuming a causal relationship, one may hypothesize that treating depression could lead to improved survival. Therefore, randomised trials in patients with a myocardial infarction and a major depressive disorder have been performed to investigate whether interventions aimed at treating the depression would also increase survival [66]. Until now, there is no evidence for any survival benefit.

Although it would have been very interesting to observe a survival benefit, treatment of depressive disorders and decreased HRQOL remains an important goals. Firstly, depressive disorders are highly prevalent in patients with diabetes [67]. Secondly, comorbid depressions affect health state of many patients with chronic diseases, but the combination of diabetes and depression has the worst effects on someone's health state [68]. Even more important, depressive disorders affect health state of a patient to a greater extent than chronic diseases [68]. Elderly patients with diabetes may consider improving quality of life much more important than adding weeks or months to their lives. Therefore, discussing treatment goals with elderly patients is imperative and should never be forgotten.

Changes over time

In **Chapter 9** the main results of the ZODIAC study during the period 1998-2008 have been described. All quality indicators, except for body mass index, have considerably improved during this period. No relevant differences between time trends were observed between the various age categories. Some striking changes were observed for the oldest elderly (>75 years). The proportion of patients using a statin in this age group increased sixteen-fold from 3.4% in 1998 to 53.3% in 2008. Another example is the decrease in mean blood pressure: 154 mmHg in 1998 versus 143 mmHg in 2008. Whether there will be further changes in the quality indicators or not, remains to be seen in the following years. Since there already have been large changes, it will become harder to establish additional changes; the so-called ceiling effect.

Bearing the lack of evidence and the vulnerability of elderly patients in mind, it should be questioned whether such large changes are a 'good' or a 'bad' thing. Does improved cardiovascular risk management lead to reduced morbidity and mortality in elderly patients with T2DM? The evidence may be compelling for younger age categories, yet in old age the efficacy of intensive cardiovascular risk management is unclear. Even more important than the possible lack of efficacy is the potential damage, that could be the result of overtreatment. A retrospective cohort study amongst patients with T2DM aged 18 years and older, showed that the prevalence of overtreatment in hypertension management was 8% [69]. Potential overtreatment was defined as a systolic blood pressure <130 mmHg and a diastolic blood pressure <65 mmHg in combination with any of the following criteria: receiving ≥3 blood

pressure medication classes, or the prescription of a new blood pressure medication class within 90 days after blood pressure measurement, or the increase in medication dosage within 90 days after blood pressure measurement. Unfortunately, the ZODIAC database does not include data on changes in medication dosage or prescription of new classes within the first months. Nevertheless, I used various definitions based on the combination of receiving ≥3 antihypertensives and a certain blood pressure level in order to estimate the possible overtreatment amongst patients >75 years in the ZODIAC study. Since the appropriate target level in old age remains a topic of debate, I have opted for several definitions (table 1). Although there is quite some variation between the estimations of overtreatment, there is no doubt that the decrease in mean blood pressure over time has also led to an increase in overtreatment. Based on the estimations, overtreatment increased from 0-1.8% in 1998 to 1.6-18.9% in 2008. Finally, the increase in use of drugs has undoubtedly led to an increase in medical costs. In times of limited financial resources, the use of costly interventions, for which limited evidence exists, should be judged very critically.

Year	Number of patients	Definition over overtreatment		
		<130/65	<140/90	<160/90
1998	503	0	0.4	1.8
1999	571	0.2	1.2	3.2
2000	436	0.7	2.5	4.0
2001	485	1.6	3.5	6.5
2002	459	0.7	3.5	7.9
2003	1094	0.4	2.9	7.0
2004	1285	0.9	4.8	11.1
2005	1210	0.9	5.9	13.2
2006	4990	1.1	6.6	14.5
2007	6356	1.4	7.5	16.9
2008	7216	1.6	8.9	18.9

Table 1. Proportion of overtreatment in hypertension management in the ZODIAC study amongst patients aged >75 years. The definitions are based on the combination of receiving ≥3 antihypertensives and a blood pressure below the levels mentioned in the table.

Frail patients: how to recognize them

As mentioned earlier, frailty is an important factor to consider when determining someone's target values and treatment strategy. But how can physicians recognize frail patients? Of course, frailty comprises a broad spectrum and patients from both ends of the spectrum, i.e. the very healthy and the very frail patients, are easy to identify. However, many patients have a frailty level that lies somewhere in between. Recognizing frailty in these patients is not that simple. Before discussing these matters, let's consider the concept of frailty first.

Frailty can be regarded as a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, and social). These losses are caused by the influence of a range of variables and increase the risk of adverse outcomes [70]. Although there are several other definitions, all these definitions have in common that frailty increases the vulnerability to adverse health outcomes [71,72]. Although frailty is related to disability and chronic diseases, it is usually regarded as a predisability state nowadays [71,73]. In the past decades, several instruments have been developed to measure frailty [73]. As a consequence, there is quite some variation in the prevalence of frailty. Amongst patients aged 75 years and older, frailty was prevalent in 47% when the 'Tilburg Frailty Indicator' (TFI) was used [73]. In a study that measured frailty with the 'Groningen Frailty Indicator' (GFI), the prevalence of frailty was 32% in a population of community-dwelling persons aged 65 years and older [74]. A recent published study that investigated the relationship between frailty and mortality in patients with diabetes used the 'Frailty Staging System' (FSS) as an index of functional impairment [75]. In the age range 65-74 years, 39% of the patients with diabetes were identified as frail subjects compared to 27% for subjects without diabetes. Remarkably, this difference in prevalence of frailty attenuated with advancing age. In the age category ≥ 75 years the percentages of frail subjects were 64% and 60% in patients with and without diabetes, respectively. This study also showed that frailty is an important predictor of mortality, and that it is even a stronger predictor in patients with diabetes [75].

In the previous sections on the several aspects of cardiovascular risk management, less intensive treatment was recommended for patients with higher levels of frailty. Although there are several validated instruments for measuring frailty, there are many unresolved issues in daily practice. For example, how frail are the elderly patients included in clinical trials of cardiovascular disease? Because someone's actual age is quite often a poor indicator of biological age [71], trials in old age should always systematically measure frailty. Translating the results to daily practice will become easier that way. Physicians only need to measure frailty in order to know whether their patient resembles the trial population. Due to the fact that physicians could consider the various frailty instruments time-consuming, measuring walking speed may be an interesting alternative. As elaborately discussed in this thesis, the role of blood pressure as a risk factor for mortality declines with advancing age. Furthermore, it was hypothesized that frailty may be an important factor. Odden et al. showed that the relationship between mortality and blood pressure is influenced by walking speed. Higher blood pressure was only associated with increased mortality among faster walkers, and no relationship was found for slow walkers [76]. The combination of weight loss or a BMI <21, two questions of the RAND-36 questionnaire, and a question about weekly exercise may also be a quick method for identifying frail patients [51]. The questions of the RAND-36 questionnaire that were used were questions on the self-reported difficulty in carrying or lifting a grocery bag and on reported low energy most or all of the time during the preceding 4 weeks.

Rather than estimating someone's frailty level at a glance, using validated frailty instruments will lead to a more objective measure of frailty with less inter-individual variation. However, the clinical use of frailty instruments remains limited until trials in old age start measuring frailty systematically.

ZODIAC: relationships, not causality

The prospective observational design of the ZODIAC study has been mentioned several times as the most important limitation of the studies as presented in this thesis. Strictly speaking, this indeed is an important limitation because observational studies only describe relationships and not causality. However, in absence of evidence from randomised controlled trials, observational studies are the next best level of evidence. The ZODIAC cohort also has an important advantage: the study population is representative of the population of patients with T2DM in daily practice. Nevertheless, it is important to realise that many other factors may explain the relationships observed in the various chapters of this thesis. Several hypotheses were formulated regarding the possible mechanisms underlying the different relationships in old age.

Patient-related hypotheses

Comorbidity and frailty may be related to changes in the traditional risk factors. Lower blood pressure is often observed in patients with heart failure. As heart failure reduces life expectancy, this may influence or even explain the relationship between blood pressure and mortality. As mentioned before in this chapter, additional adjustment for a surrogate variable of heart failure did not change the inverse relationship. Furthermore, lower lipids may be a signal of occult disease. The results between all-cause mortality and glycemic regulation may be confounded by a diagnosis of cancer or anaemia. In an Italian cohort the relationship between HbA1c and cardiovascular outcomes was affected by the level of comorbidity: patients in the high comorbidity group experienced no benefit from lower HbA1c levels [77]. The phenomenon that comorbidities and frailty may influence the relationship between the risk factor in question and mortality, is called 'reverse causality'.

Another explanation for the different outcomes of risk factors in old age may be that risk factors simply are not that important in old age. Subjects surviving long enough with (for example) a high cholesterol may be (and definitively have been) less susceptible to its adverse consequences. Also, a moderately decreased renal function could be a physiological phenomenon. Perhaps this is why it was not related to an increased mortality risk.

Treatment-related hypotheses

The use of drugs such as antihypertensive agents may have resulted in confounding by indication. In the ZODIAC-12 study (**Chapter 4**) additional analyses were performed in which we stratified according to the use of antihypertensive agents. The results were different between these two groups, and this may imply two things. Firstly, it can be seen as a confirmation of the confounding by indication bias: patients who used antihypertensive drugs in 1998 were at higher risk for cardiovascular disease than the patients who did not use these drugs. Secondly, the inverse relationship between blood pressure and mortality in the group that received antihypertensive drugs, may also imply that treatment itself have caused the increased mortality risk. A possible mechanism by which treatment could have led to increased mortality is excessive lowering of blood pressure, which in turn may have led to fall incidents.

We observed no association between blood pressure and mortality in elderly patients without antihypertensive medication. Since confounding by indication plays no role in this population, these results are probably more resistant to this bias. In other words: blood pressure is not a marker of mortality in elderly patients without antihypertensive medication, and in patients with hypertension as comorbidity, blood pressure is even inversely related to mortality. Confounding by indication plays a less important role in the relationship between lipids and mortality as only a few patients received lipid lowering treatment at the start of the observation period (15 out of the 326 patients >75 years). As a consequence, the relationship between lipids and mortality probably reflects the true effects of lipids as a risk factor of mortality.

Conclusion

The general aim of this thesis was to study several aspects of diabetes care, specifically in old age, in order to provide evidence that can aid in clinical decision-making in daily practice and in tailoring important aspects of the guidelines for T2DM to this specific population. Based on the various chapters of this thesis it can be concluded that for elderly patients with type 2 diabetes:

1. traditional cardiovascular risk factors have other consequences with respect to mortality when compared to younger patients.
    - Lower blood pressure is related to higher mortality. Adjustment for a surrogate variable of heart failure (MR-proANP) did not influence this inverse relationship.
    - Poor glycemic control is related to increased cardiovascular mortality, but not to all-cause mortality. Subanalyses showed that the relationship between glycemic control and mortality is limited to patients with diabetes of short duration.
    - Higher lipids are not related to increased mortality, except for patients with diabetes of long duration.

- Based on these different observational relationships, and the lack of evidence from randomised controlled trials in old age, other target values and/or treatment strategies are necessary.

2. lower quality of life is independently related to increased mortality. Although it is unknown whether attempts at improving quality of life will lead to a better life expectancy, quality of life is also an important treatment goal.

3. a moderately decreased renal function (eGFR 45-60) is not associated with increased mortality. Therefore, an eGFR 45-60 should be considered as physiological in elderly subjects with diabetes at first.

4. orthostatic hypotension is highly prevalent (28%). It was remarkable that orthostatic complaints, but not orthostatic hypotension, were related to an increased risk of falling.

5. quality of diabetes care has considerably improved during the period 1998-2008. However, it remains unknown whether these changes over time will also lead to reductions in morbidity and mortality.

Based on the results of this thesis and the lack of evidence from randomised trials, I have come to the conclusion that current treatment strategies, as advised in various guidelines, are to a large extent not evidence-based. Therefore, health care providers should loosen the reins on treatment goals of elderly patients with T2DM unless there are clear arguments for strict treatment.

Recommendations

The following recommendations for daily practice and future research will lead, in my opinion, to better and more evidence-based diabetes care in old age.

1. *Target values should be individualized.* Health care providers should be working with individualized target values instead of using target values that are advocated in the guidelines. The current guidelines advocate (intensive) treatment, except when there are clear arguments for not doing so. This thesis supports the opposite: less stringent treatment unless there are evidence-based arguments for strict treatment. This attitude is in line with the fundamental medical principle that the patient's well-being is the primary consideration, especially when the efficacy of an intervention is questionable: primum non nocere.

2. *Aim of diabetes care should be individualized.* The aim of diabetes care should be individualized according to the goal that is the most important for that specific patient. For some patients this could be quality of life, for others this could be an optimal cardiovascular risk profile. Although this thesis focussed on mortality, there are many other endpoints that are highly relevant to the elderly patient. Instead of measuring cardiovascular morbidity and mortality, future studies should consider investigating other endpoints, including quality of life, the ability to live independently, or cognitive functioning. The DANTE study that has been initiated to study the effects of discontinuing antihypertensive treatment on cognitive functioning is a good example of this [78].

3. *Age-related quality indicators should be used for benchmarking purposes.* Using the same quality indicators for all age categories does not reflect the goal of using these indicators in the first place, which should be contributing to improving diabetes care. Take for example blood pressure treatment in old age. The outcome measure that measures the proportion of patients who have a systolic blood pressure below the target value should use a cut-off value of 160 mmHg for patients >75 years. This value is more evidence-based than the value of 140 mmHg that is currently used. As published before, quality indicators suggesting overtreatment should also be introduced. An HbA1c <7% in combination with insulin can be regarded as a sign of poor care [79].

4. *Inquiring after orthostatic complaints should become standard of care.* Recognizing at least part of the patients who have an increased risk of falling may be as simple as inquiring after orthostatic complaints. Besides the fact that measuring OH is time-consuming and therefore difficult to perform routinely in daily practice, OH was also not related to falling. Because orthostatic complaints were associated with falling, more studies are needed to confirm our findings and to investigate whether interventions, aimed at reducing orthostatic complaints, are beneficial in reducing fall incidents.

5. *Other definitions of orthostatic hypotension should be investigated.* This thesis showed that OH was not related to falls and/or fall risk. As the definition of OH should be based on its associations with adverse health outcomes, prospective studies need to be performed to evaluate the prognostic properties of the different definitions of OH.

6. *Pragmatic trials are necessary to facilitate clinical decision-making in daily practice.* The effectiveness of interventions in the real-world population may be different when compared to the results of studies using many eligibility and exclusion criteria [80]. Therefore, randomised controlled trials investigating cardiovascular risk interventions in populations resembling the real-world population as close as possible are necessary in order to reduce the effects of selection bias.

7. *Randomised trials in old age should always contain frailty indicators.* As long as trials in old age do not contain validated frailty indications, it remains very difficult for health care providers to translate the results of studies amongst elderly patients to their population or individual patients.

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Chapter 12

Summary

The worldwide prevalence of type 2 diabetes mellitus is high and still increasing [1-3]. Although obesity and lifestyle are the most important contributors, ageing of the Western population also contributes to the current diabetes epidemic. In the 'Zwolle Outpatient Diabetes project Integrating Available Care' (ZODIAC) study, a shared care project for patients with type 2 diabetes mellitus (T2DM), more than one quarter of the participating patients is older than 75 years. Very little is known about the effectiveness of different (drug) interventions to prevent cardiovascular morbidity and mortality in this specific population. Unfortunately, there are no randomised controlled trials that have specifically investigated the effects of any cardiovascular risk modifying intervention for diabetic patients older than 75 years. Also, there is an underrepresentation of elderly patients in clinical trials of cardiovascular disease [4,5]. Based on the absence of evidence and the specific characteristics of the elderly population, the question arises whether the goal of diabetes management should be the same for elderly patients as it is for younger patients. The general **aim of this thesis** was to study several aspects of diabetes care for this specific population, in order to provide evidence that can aid in clinical decision-making in daily practice and in tailoring important aspects of the guidelines for patients with T2DM to this specific population. A large part of this thesis is based on the ZODIAC study, a prospective observational cohort study of patients with T2DM who are treated in primary care. Data from the ZODIAC study have been used to investigate the prognostic capabilities of several cardiovascular risk factors and quality of life in old age, but also to describe the changes in diabetes care in the period 1998-2008 for different age categories. The prevalence of orthostatic hypotension and its associations with falls have been assessed in a cross-sectional study. The different chapters of this thesis will be summarized below.

The association of glycemic control with mortality was assessed in **Chapter 2**. In the total group of elderly patients poor glycemic control was related to an increased cardiovascular mortality risk. Additional analyses showed that poor glycemic control only had prognostic value for patients with a diabetes duration less than 5 years. These results correspond with previous randomised controlled trials that showed that, with respect to mortality, intensive glucose control may only be beneficial in those with diabetes of short duration [6-9].

Chapter 3 aimed to investigate the relationship between lipids and mortality in old age. Higher levels of LDL-cholesterol and a higher cholesterol-HDL ratio were not associated with an increased mortality risk for the overall group of elderly patients. The only significant relationship that was observed, was for triglycerides: higher levels were associated with less all-cause mortality. As with glycemic control, diabetes duration had an important impact on the relationship between lipids and mortality. Higher lipids were related to increased cardiovascular mortality for patients with a diabetes duration of 8 years and longer. As occult disease or declining health may explain the inverse relationship between triglycerides and

mortality, additional analyses were performed in which the deaths in the first years of follow-up were excluded [10]. The results were not relevantly different.

The results as presented in **Chapter 4** showed that blood pressure has important prognostic value in old age. However, this relationship is quite the opposite as one may expect. The mortality risk declined with higher blood pressure values. Various explanations have been proposed for this inverse relationship. As low blood pressure is often seen in patients close to death, additional analyses were performed in which the deaths early in follow-up were excluded. The results were not different. Heart failure is another explanation that has been proposed as an explanation for the inverse relationship [11]. Therefore, we have additionally adjusted for heart failure by using the mid-regional fragment of pro-A-type natriuretic peptide (MR-proANP) in **Chapter 5**. Again, the results were not different. MR-proANP itself was an independent marker of all-cause and cardiovascular mortality in all age categories, but its predictive capabilities did decrease with advancing age.

Moderately decreased renal function is not associated with an increased mortality risk in old age. This conclusion was drawn from the results presented in **Chapter 6**. An estimated glomerular filtration rate (eGFR) <45 ml/min/1.73m^2 was associated with higher mortality, whereas an eGFR 45-60 was not. Albuminuria was an important marker of mortality in old age, irrespective of eGFR. These results confirm that a moderately decreased renal function should be considered as physiological at first. The Dutch national transmural agreement (LTA) for 'Chronic renal impairment' already promotes the use of age-related cut-off values for renal function. Using these cut-off values will result in more targeted referral to secondary care, especially for the elderly [12].

Chapter 7 showed that health-related quality of life (HRQOL) is an independent marker of all-cause and cardiovascular mortality in elderly patients. These results are of special interest because the goal of treatment in old age may be different compared to younger patients. Improving or maintaining quality of life could be more relevant for a specific patient than aiming to reduce risk of complications and their associated mortality. Whether attempts at improving HRQOL will also lead to a better life expectancy remains to be determined.

A cross-sectional observational study to study the prevalence of orthostatic hypotension (OH) and its association with different clinical variables, amongst others diabetes and falling, was undertaken between January 2009 and May 2010. The results of this study are described in **Chapter 8**. The prevalence of OH was 28% and 18% in patients with and without T2DM, respectively. It was remarkable that orthostatic complaints, but not orthostatic hypotension, were related to an increased risk of falling, even after adjustment for orthostatic hypotension.

The changes over time in quality of diabetes care, within the ZODIAC study, for a wide variety of quality measures was investigated in a study presented in **Chapter 9**. The number of patients participating in the ZODIAC study, a shared care project, increased from 1622 in 1998 to 27.438 in 2008. All quality indicators improved in this study, except for body mass index and serum creatinine. No relevant differences between trends for separate age categories were observed. For patients aged older than 75 years some striking changes were observed. Whether the large improvements in old age will lead to reductions in morbidity and mortality remains to be determined.

In anticipation of the general discussion of this thesis (**Chapter 11**), a perspective on blood pressure treatment and target values in old age was presented in **Chapter 10**. Selection bias that often occurs in randomised controlled trials was illustrated by comparing the mortality rate in the ZODIAC study, an unselected primary care population, to the population of the ADVANCE study, a large trial amongst patients with T2DM [13]. Only patients older than 75 years were selected for this comparison. After a follow-up period of approximately 5 years, 19% of the study population had died in the ADVANCE study, compared to 35% in the ZODIAC cohort. Because of the limited evidence that supports antihypertensive treatment in old age, a systolic target value of 160 mmHg was proposed for the majority of elderly patients with T2DM.

Based on the results of this thesis and the lack of evidence from randomised trials, I have come to the conclusion that current treatment strategies, as advised in various guidelines, are to a large extend not evidence-based. Therefore, health care providers should loosen the reins on treatment goals of elderly patients with T2DM unless there are clear arguments for strict treatment.

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Chapter 13

Nederlandse samenvatting

(summary in Dutch)

Introductie

De prevalentie van diabetes mellitus is hoog en neemt in de komende jaren alleen maar toe Twee decennia geleden werd nog voorspeld dat het aantal patiënten met diabetes in Nederland zou toenemen van 200.000 in 1990 tot 350.000 in 2005 [1]. Het daadwerkelijke aantal patiënten met diabetes bleek in 2005 tweemaal zo hoog te zijn, en in 2007 werd het aantal patiënten zelfs geschat op 740.000. De verwachting is dat de prevalentie in 2025 zal toenemen tot 1.6 miljoen. Ruim een kwart van alle patiënten met diabetes mellitus type 2 (DM2) is ouder dan 75 jaar. Hoewel het nut van de behandeling van diabetes en van andere risicofactoren van hart- en vaatziekten voor jongere patiënten onomstreden is, geldt dit niet voor de groep ouder dan 75 jaar. Juist deze groep patiënten wordt niet meegenomen in grote wetenschappelijke studies naar bijvoorbeeld de effecten van intensieve glucoseregulatie of bloeddrukverlaging. Daarnaast zijn de oudere patiënten die wél hebben meegedaan aan deze studies vaak erg vitaal en dus niet representatief voor de grote groep ouderen. Het is dan ook maar de vraag in hoeverre de huidige richtlijnen en behandelstrategieën van toepassing zijn op deze groeiende groep patiënten. Het doel van dit proefschrift was om verschillende aspecten van de dagelijkse zorg voor ouderen met DM2 meer wetenschappelijk te onderbouwen. Een belangrijk deel van het proefschrift is gebaseerd op de ZODIAC-studie, een prospectieve observationele cohort studie van patiënten met DM2 die in de eerstelijns-gezondheidszorg werden behandeld. Gegevens van de ZODIAC-studie zijn gebruikt om te onderzoeken in welke mate diverse risicofactoren voor hart- en vaatziekten ook bij ouderen voorspellend zijn van sterfte. Daarnaast is er bij ruim 500 mensen gekeken hoe vaak orthostatische hypotensie voorkomt en of er een relatie is met vallen.

Samenvatting

In **Hoofdstuk 2** is de relatie tussen de glycemische regulatie en sterfte onderzocht. Het risico om te overlijden aan cardiovasculaire oorzaken nam met 26% toe (95% betrouwbaarheidsinterval 6-49%) bij elke toename van het HbA1c met 1%. Een slechte glycemische regulatie was alleen bij patiënten met een korte diabetesduur (<5 jaar) voorspellend van sterfte. Deze resultaten komen overeen met een aantal grote gerandomiseerde studies bij jongere patiënten [2-5]. Een intensieve glucoseregulatie lijkt alleen maar gunstige effecten op het sterfterisico te hebben bij patiënten met een korte diabetesduur. Hoewel het verbeteren van de glycemische regulatie bij ouderen met een korte diabetesduur mogelijk zinvol is, is het belangrijk om te realiseren dat er in het algemeen minder intensieve streefwaarden gehanteerd moeten worden. Allereerst is er een gebrek aan gerandomiseerde studies bij ouderen. Daarnaast duurt het zeker meerdere jaren om diabetesgerelateerde complicaties te ontwikkelen [6,7]. Het risico van hypoglycemieën is een andere belangrijke overweging om voorzichtig te zijn. Een

streefwaarde van 64 mmol/mol (8%) lijkt een prima streefwaarde voor de meerderheid van de patiënten ouder dan 75 jaar. Een intensievere behandeling kan overwogen worden voor de vitale oudere met een korte diabetesduur. Voor kwetsbare ouderen met veel comorbiditeit en een verminderde levensverwachting kunnen hogere waarden worden geaccepteerd.

De resultaten die zijn beschreven in **Hoofdstuk 3** laten zien dat diabetesduur ook een grote invloed heeft op de relatie tussen het vetspectrum en sterfte. Hoewel in de totale groep 75-plussers geen relatie met sterfte werd aangetoond, bleek dat bij patiënten met een diabetesduur van 8 jaar of meer hogere waardes van het LDL-cholesterol geassocieerd waren met toegenomen cardiovasculaire sterfte. In de dagelijkse praktijk krijgen ouderen met DM2 steeds vaker een statine voorgeschreven. De richtlijn 'verantwoorde diabeteszorg bij kwetsbare ouderen' van Verenso (vereniging van specialisten ouderengeneeskunde en sociaal geriaters) adviseert om bij alle ouderen een statine voor te schrijven, tenzij de levensverwachting 2 jaar of minder is [8]. Er zijn echter meerdere argumenten voor een terughoudender beleid. Allereerst neemt de waarde van het vetspectrum als een risicofactor voor hart- en vaatziekten af met het ouder worden [9]. Een gebrek aan gerandomiseerde studies en selectiebias spelen ook hier een grote rol. Tot slot moet ook de invloed van mogelijke bijwerkingen, zoals spierklachten en negatieve effecten op de cognitie, niet worden onderschat [10-14].

In **Hoofdstuk 4** is aangetoond dat bij ouderen met DM2 het sterfterisico afneemt naarmate de bloeddruk hoger wordt. In de leeftijdscategorie 60-75 jaar werd geen relatie tussen bloeddruk en sterfte gevonden. Aangezien hartfalen de omgekeerde relatie tussen bloeddruk en sterfte zou kunnen verklaren, werden de extra analyses uitgevoerd zoals die in **Hoofdstuk 5** zijn beschreven. Bij een correctie voor MR-pro-ANP, als een surrogaat variabele voor hartfalen, veranderden de resultaten echter niet. Er zijn verschillende mogelijkheden die de inverse relatie op oudere leeftijd kunnen verklaren. Kwetsbaarheid en comorbiditeit kunnen een belangrijke rol spelen. Ook bijwerkingen van antihypertensiva en het overmatig verlagen van de bloeddruk zijn mogelijke verklaringen.

Een beperkt verlaagde nierfunctie op oudere leeftijd komt veelvuldig voor en kan volgens sommigen worden gezien als onderdeel van het fysiologische verouderingsproces. Volgens anderen is het een teken van de hogere prevalentie van chronische nierinsufficiëntie bij ouderen [15]. De resultaten in **Hoofdstuk 6** tonen dat een beperkt verlaagde nierfunctie (MDRD 45-60 ml/min/1.73m2) niet geassocieerd was met totale en cardiovasculaire sterfte. Albuminurie daarentegen bleek ook op hoge leeftijd een onafhankelijke voorspeller van sterfte. Deze resultaten bevestigen de leeftijdsafhankelijke afkapwaarden zoals die gehanteerd worden in de Landelijke Transmurale Afspraak 'Chronische nierschade' [16]. Het achteruitgaan van de nierfunctie in de loop van de tijd en de aanwezigheid van albuminurie zijn daarentegen wel aanwijzingen voor het bestaan van chronische nierinsufficiëntie.

In dit proefschrift is de RAND-36 vragenlijst gebruikt om kwaliteit van leven te meten. Deze vragenlijst bestaat uit 36 vragen die betrekking hebben op 9 dimensies van kwaliteit van leven. Deze dimensies kunnen worden verdeeld in 2 samenvattende schalen voor respectievelijk de fysieke en mentale kwaliteit van leven. Deze schalen kunnen worden gezien als een maat voor de fysieke beperkingen en depressieve klachten. Zowel de totaalscore van de RAND-36, als de samenvattende schalen, waren onafhankelijke voorspellers van sterfte bij ouderen met DM2 (**Hoofdstuk 7**). De RAND-36 vragenlijst lijkt ook geschikt te zijn als een maat voor de kwetsbaarheid van ouderen [17]. Patiënten die volgens de vragenlijst kwetsbaar waren, hadden een verminderde overleving, liepen langzamer en hadden meer fysieke beperkingen. Afgezien van het feit of het verbeteren van de kwaliteit van leven ook gunstige effecten heeft op de overleving, is kwaliteit van leven natuurlijk ook een doel op zichzelf. Het toevoegen van leven aan de dagen kan door ouderen veel belangrijker worden gevonden dan het toevoegen van dagen aan het leven.

In de discussie over de behandeling van hypertensie op oudere leeftijd spelen mogelijke bijwerkingen van antihypertensiva een belangrijke rol. Orthostatische hypotensie (OH) is een mogelijke bijwerking en wordt geassocieerd met een hoger risico om te overlijden aan ongevallen en letsels [18]. De cross-sectionele studie in **Hoofdstuk 8** bevestigde de veronderstelling dat de prevalentie van OH onder thuiswonende ouderen met DM2 hoog is (28%). Hoewel er geen relatie werd aangetoond tussen vallen en OH, waren orthostatische klachten wel geassocieerd met een hoger valrisico en eerdere valincidenten. Het actief informeren naar klachten die passen bij orthostase is een simpele interventie en lijkt zinvoller te zijn dan het meten van OH.

Hoofdstuk 9 beschrijft de ontwikkelingen van de kwaliteit van de geleverde diabeteszorg in de periode 1998-2008. Het aantal deelnemende patiënten aan de ZODIAC-studie is gestegen van 1622 in 1998 tot 27.438 in 2008. Er werden grote verbeteringen voor alle kwaliteitsindicatoren, behalve de body mass index, waargenomen, waarbij de trends in de loop der tijd sterk significant waren. Er werden geen verschillen gevonden in de trends tussen de verschillende leeftijdscategorieën. Al met al is de kwaliteit van de diabeteszorg in de periode 1998-2008 dus sterk verbeterd. Of deze veranderingen ook voor de oudere patiënten daadwerkelijk zullen leiden tot minder hart- en vaatziekten en een verbeterde levensverwachting blijft vooralsnog onduidelijk.

In **Hoofdstuk 10** wordt een voorstel gedaan om bij ouderen met DM2 andere streefwaarden voor de systolische bloeddruk te hanteren: 160 mm Hg, tenzij er argumenten zijn voor meer intensieve behandeling. Er is slechts één grote gerandomiseerde studie (ADVANCE) die specifieke analyses heeft uitgevoerd voor 75-plussers met diabetes [19]. De in deze studie geïncludeerde patiënten hadden naast DM2 nog een extra risicofactor voor hart- en

vaatziekten. Een indicatie voor behandeling met insuline was een exclusiecriterium om deel te nemen aan deze studie. Het risico om te overlijden aan cardiovasculaire oorzaken was 35% lager ten opzichte van de placebogroep. Hoewel deze studie dus gunstige effecten laat zien van het verlagen van de bloeddruk op oudere leeftijd, is het maar de vraag in hoeverre deze resultaten ook van toepassing zijn op de gemiddelde populatie ouderen met DM2. Selectiebias lijkt namelijk een grote rol te spelen in de ADVANCE-studie. De patiënten in de ZODIAC-studie hebben namelijk een sterfterisico dat tweemaal hoger is dan in de controlegroep van de ADVANCE-studie. Voor vitale patiënten met DM2 die nog niet behandeld worden met insuline moet een streefwaarde van 140 mm Hg worden overwogen. Een streefwaarde van 160 mm Hg lijkt daarentegen een prima waarde te zijn voor alle andere patiënten.

Conclusie

Voor oudere patiënten met DM2 kan worden geconcludeerd dat:

1. traditionele risicofactoren voor hart- en vaatziekten andere consequenties hebben dan bij jongere patiënten.
2. een verminderde kwaliteit van leven gerelateerd is aan toegenomen sterfte.
3. een beperkt verlaagde nierfunctie niet geassocieerd is met toegenomen sterfte en daarom in eerste instantie als fysiologisch beschouwd kan worden.
4. de prevalentie van orthostatische hypotensie hoog is, maar dat alleen het hebben van orthostase klachten gerelateerd is aan een hoger valrisico en eerdere valincidenten.
5. er grote veranderingen hebben plaatsgevonden in de geleverde diabeteszorg in de periode 1998-2008. Het blijft echter onduidelijk of er hier ook daadwerkelijk gesproken kan worden van een kwaliteitsverbetering.

De hoofdconclusie van het proefschrift is dat de huidige behandeling van DM2 bij ouderen slecht onderbouwd is en dat nadelige effecten van behandeling niet kunnen worden uitgesloten. Bij het gros van de ouderen met DM2 kan de behandeling van de diabetes zelf, maar ook van de andere risicofactoren voor hart- en vaatziekten, minder streng. Daarnaast is het bij ouderen erg belangrijk om te kijken naar het doel van behandelen. Heeft het zin om te streven naar een zo laag mogelijk risico van hart- en vaatziekten? Of is het streven naar een optimale kwaliteit van leven veel belangrijker? De geschatte levensverwachting en kwetsbaarheid van de ouderen zijn hierbij belangrijke factoren om te overwegen. De belangrijkste aanbevelingen van dit proefschrift zijn dat het noodzakelijk is dat behandeldoelen en streefwaarden worden geïndividualiseerd.

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Previous dissertations at our Diabetes Centre:

- **Gerrits E.G.** (2013). *Cardiovascular risk and its determinants in high risk patients.* Promotores: Prof. dr. H.J.G. Bilo, Prof. dr. R.O.B. Gans. Copromotores: Dr. A.J. Smit, Dr. H.L. Lutgers.
- **Landman G.W.** (2012). *Mortality predictors in patients with type 2 diabetes.* Promotores: Prof. dr. H.J.G. Bilo, Prof. dr. R.O.B. Gans. Copromotores: Dr. N. Kleefstra, Dr. K.H. Groenier.
- **Lenters-Westra W.B.** (2011). *Hemoglobin A1c: Standardisation, analytical performance and interpretation.* Promotores: Prof. dr. H.J.G. Bilo, Prof. dr. R.O.B. Gans. Copromotores: Dr. R.J. Slingerland.
- **Kleefstra N.** (2010). *Self-care interventions in type 2 diabetes.* Promotores: Prof. dr. H.J.G. Bilo, Prof. dr. R.O.B. Gans. Copromotores: Dr. S.T. Houweling, Dr. K.H. Groenier.
- **Logtenberg S.J.J.** (2010). *Intensive insulin therapy and glucose management. Studies with the implantable pump and a glucose sensor.* Promotores: Prof. dr. H.J.G. Bilo, Prof. dr. R.O.B. Gans.
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- **Hart H.E.** (2004). *Health related quality of life in patients with diabetes mellitus type I.* Promotoreres: Prof. dr. M. Berg, Prof. dr. B. Meyboom-de Jong. Copromotor: Dr. H.J.G. Bilo.
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- **Goddijn P.P.M.** (1997*). Improving metabolic control in NIDDM patients referred for insulin therapy.* Promotor: Prof. dr. B. Meyboom-de Jong. Copromotor: Dr. H.J.G. Bilo.

List of publications

- van Hateren KJ, Landman GW, Kleefstra N, Groenier KH, Struck J, Navis GJ, Bakker SJ, Houweling ST, van der Meer K, Bilo HJ. The midregional fragment of pro-A-type natriuretic peptide, blood pressure, and mortality in a prospective cohort study of patients with type 2 diabetes (ZODIAC-25). Diabetes Care 2012 Dec 10; Epub ahead of print.
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